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PAIN MANAGEMENT IN THE NEONATE

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Editorial

Editorial: Measuring and managing pain in the fetus and neonate - A new era and new challenges

In just over three decades, our understanding of the effects of pain in the fetus and newborn has grown immensely. We have progressed from believing that, because of their anatomical and physiological immaturity, neonates were incapable of experiencing pain and responding to painful stimuli [1], to a point where the importance of pain management in neonates is now universally acknowledged. However, while we seek to minimise painful interventions as much as possible, for the majority of babies receiving life-saving intensive care, potentially painful procedures are an unavoidable daily occurrence highlighting the importance of this aspect of care [2]. We have had, for some time in our repertoire, a number of tools for the assessment and management of acute pain [3], though fewer to assess persistent pain [4]. Still the subjective nature of pain makes it challenging, no tool appears perfect, and many important questions remain unanswered. Recent years have seen greater awareness of the importance of preventing and treating pain in babies, yet even in areas where concerted efforts have been made to try to optimise and standardise management, such as the use of pre-medication for endotracheal intubation, translation of evidence into practice has been limited [5]. In addition, advances in science and technology, whilst welcomed, mean that we have to constantly reconsider and anticipate the potential effects of these changes in management on the comfort of our tiny patients. Clinical practice with respect to identification, assessment and treatment of pain remains extremely varied between and within neonatal units worldwide [6,7]. The search therefore continues for optimum ways of recognising and managing pain in vulnerable and sick preterm and term born neonates.

In this issue, we bring together contributions from leading researchers in the field of neonatal pain, to provide up-to-date reviews of current research, practice and progress in this important area of neonatal care. In an account that will be important for both neonatal and obstetric practitioners, Bellieni first reminds us that the perception of pain begins in utero, and describes the very earliest responses to stimuli even before birth. Measuring pain in early life is challenging because of the lack of self-report in pre-verbal infants. There is a need for accurate means of pain assessment that are not at risk of subjective bias and methods with the potential to provide greater objectivity are currently being explored. Gurzul and colleagues discuss novel methods of measuring pain-associated brain activity using a variety of different modalities, Vento addresses the potential of biochemical markers of pain and stress, while Eriksson and Campbell-Yeo explore pain assessment in the clinical setting. With respect to the management of pain in the newborn infant, Pillai Riddell discusses how the use of drugs to treat pain might be minimised by employing non-pharmacological methods, while Van den Hoogen and colleagues consider how knowledge of neurodevelopmental biology can guide the pharmacological management of pain, when this is warranted. There has been a sea change in recent years in the respiratory management of preterm babies, and evidence suggests that the use of less invasive methods of respiratory support is desirable [8]. Yet this brings with it new challenges, and demands a different approach to maintaining babies' comfort without compromising respiratory status, as considered by Tauzin and Durrmeyer. Walker reminds us that untreated or poorly managed pain in early life is not benign. She considers how early experiences of pain can influence later experiences and responses and importantly, suggests how, as neonatal clinicians, we can mitigate against these long-term adverse effects. Finally, Garten and Bührer focus on the important issue of palliative care in the neonatal unit and how we can ensure comfort and dignity for the most vulnerable babies under our care at the end of their lives.

We have come a long way in our learning, and in advocating for the rights of our smallest patients for the alleviation of pain in neonatal intensive care. Nevertheless, there is still a distance to go and we should not be complacent. This issue provides some suggestions for the direction of future travel, and certainly food for thought.

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Elaine M. Boyle
University of Leicester, Department of Health Sciences, George Davies Centre, University Road, Leicester LE1 7RH, UK
E-mail address: eb124@leicester.ac.uk.

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New insights into fetal pain

Carlo V. Bellieni[*]

Neonatal Intensive Care Unit, University Hospital of Siena, Italy

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ABSTRACT

Fetal pain is difficult to assess, because the main feature needed to spot pain, is the subject's capability of declaring it. Nonetheless, much can be affirmed about this issue. In this review we first report the epochs of the development of human nociceptive pathways; then we review since when they are functioning. We also review the latest data about the new topic of analgesia and prenatal surgery and about the scarce effect on fetal pain sentience of the natural sedatives fetuses produce. It appears that pain is a neuroadaptive phenomenon that emerges in the middle of pregnancy, at about 20–22 weeks of gestation, and becomes more and more evident for bystanders and significant for the fetus, throughout the rest of the pregnancy.

1. Introduction

Fetal pain is one of the most debated issues in medicine: in fact, it is very difficult to determine if a subject who cannot express its own feelings is actually experiencing pain after a potentially noxious stimulus. The international definition of the word ‘pain’, made by the International Association for the Study of pain (IASP) is not of help in this case: in fact it says that pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. This definition has been criticized because it does not include those subjects who are not aware of their own body or cannot describe it, such as mentally challenged people or babies. In short, pain has wider borders than those of standard definitions. Nonetheless, to feel pain, some basic requisites should be present [2]. They are, in order from the periphery to the center of the nervous system: a) nociceptors, b) pain neurotransmitters, c) centripetal fibers that lead the stimulus to the brain, d) the thalamus, e) connection with the cortex. Some authors argue that the thalamo-cortical connections are essential to feel pain [3], while others say that the connections from the spinal cord to the thalamus are enough, even though they allow pain to be felt only at a subconscious level. In the fetus, the cortex is relatively underdeveloped, but it is rudimentally present from the 20th week of gestation; meanwhile, a transitory structure takes the place of the cortex: the subplate. Here we review if these structures are present and active in the fetus and then analyze when their functions start.

1.1. Setting and development of nociceptive pathways in the fetus

Nociceptors are extensively present in the fetus’ skin, at least at the same density than in adults. Their axons reach the skin between 11 and 15 weeks of gestational age (WGA) and the mucosae at 20 WGA [4] after having formed synapses with the ascendant pathways in the dorsal horn of the spine at 6 WGA [5]. Most of these nerves will be precociously myelinated, starting between 12 and 14 WGA, guaranteeing a higher conduction speed of the impulse they carry to the brain [6]. Even pain neuromediators like substance P and enkephalins appear early, at 8–10 and 12–14 WGA respectively [7]. The production of endogenous opioids starts in the brain around the middle of pregnancy [8].

The spinothalamic tract is a major ascending pathway required for the normal processing of pain, temperature and itch. It is well established in fetal life, with little differences throughout the life of mammals [9]. The mesodiencephalon [brain stem, insula and thalamus] in intact fetuses shows signs of sufficient maturation starting from the 15th week of gestation [10]. Another important structure is also present in fetal life: the amygdala. The amygdala is the center of fear and anxiety in mammals, and its early appearance [11] could be a sign that even these sensations, albeit rudimental, can be felt in utero.

Direct thalamocortical fibers appear at the beginning of the second half of the pregnancy (23–30 WGA), reaching in large numbers the subplate – which they had started to colonize at 12 WGA - at 24 WGA [12]. The subplate is an important fetal structure; it is an active though transient layer of the human brain cortex between 10 and 35 WGA, capable of processing thalamic information and of contributing to transient cortical circuits [13]. It has a pivotal role in the development of the mature cortex, appearing as an intermediate station for the neurons which are colonizing the grey matter, the first cortical neurons to respond to sensory stimuli [14]. Between 24 and 32 WGA,

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[*] Neonatal Intensive Care Unit, Policlinico Le Scotte, Viale M Bracci, 36, 53100, Siena, Italy.
E-mail address: cvbellieni@gmail.com.

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thalamocortical fibers converge on various areas of the mature cortex, completing this process after 34 WGA [15].

The process of cortex formation starts in the first trimester of pregnancy, with the migration of the neurons from the depth of the brain up to the periphery, and the appearance of characteristic folds on the brain surface. The first folds can be seen at 13–15 WGA, and among them the fold which gives birth to the insula, one of the main sites for pain perception, is visible [16]. The cortex is supposed to be the center of conscious activity, and its absence would rule out any conscious pain sensation; nonetheless, it seems that some conscious sensation may be possible even with an immature cortex [17], and consequently even pain at a more or less conscious level can be felt. If even hydranencephaly, with the almost total absence of the cortex, does not preclude infants the ability to discriminate stimuli, receiving even visual information, and feeling fear, then the cortex is not so essential in elaborating, at some level of consciousness, the information it receives [18,19]

1.2. *Efficiency of the nociceptive pathways in the fetus*

Since the fetus has a sufficiently developed nociceptive system, it is important to assess if this system is active and operational. The answers to this question arrive from behavioral observation, and from either electrophysiological or endocrine responses to potentially nociceptive stimuli. Three main signs show the possibility that at a certain point of the pregnancy, the fetus may feel pain, and we will describe them in this paragraph. Firstly, its extensive reaction to external stimuli, that can make them suddenly change their behavioral state, even waking them up from sleep. Second, the changes in behavioral patterns and specific EEG pain-related features. Third, the rise in fetal blood stress hormones, after a painful stimulus to the fetus.

Fetuses can respond to external stimuli, showing sensitivity to noise, light or tactile impulses [20]. After 26 WGA their generalized movements are replaced by more coordinated responses of the head and limbs. Fetal expressions of actual crying have been registered [21], such as the blink-startle responses to sudden noises, at 30 WGA [22], as well as an avoidance reaction from 8 WGA. Ultrasound is a useful tool to detect differentiated behavioral states and even pain signs [23]. Fetuses show, at the end of pregnancy, well-established sleep-wake cycles [24]; they spend 9–21% of the time at term in active wake [25] and they can be awoken after being stimulated. States F3 (calm wake), F4 (active wake) and the state F5 (crying) are described in fetuses [26], and at 30 WGA a frank wake EEG can be recorded in prenatally born fetuses [27]. The environment within the womb is supposed to have some sedative property, because of some neuroinhibiting substance present there. These substances are adenosine, progesterone, allopregnenolone, pregnenalone and prostaglandin D2. Adenosine is a purinergic messenger, regulating many physiological processes in excitable tissues, namely in the brain. Prostaglandin D2 is a sleep-inducing hormone that induces adenosine release and the consequent GABAergic inhibition of wake-inducing neurons. Pregnanolone and allopregnenolone have an analgesic effect as well: they also increase the activity of GABA inhibitory pathways in the central nervous system. Progesterone, and its pregnane metabolites, are strongly implicated as inhibitory modulators of fetal EEG activity and behavioral state. The blood levels of allopregnenolone are similar in mothers' and fetal blood [28], while pregnanolone sulfate values are far higher in fetal blood in one study [28], but its isomers appear at similar levels in maternal and fetal blood [29]. Adenosine levels are higher in normal fetuses than in non-complicated pregnant women's blood [30], but in women with hyperhemesis gravidarum it is far higher than in fetal blood [31] (Fig. 1). PGD2 synthase concentration in human amniotic fluid appears to increase during gestational weeks 12–25 but it declines slowly until term [32]. Average progesterone is twice as high in fetuses than in mothers [33], but also in preeclamptic mothers progesterone is twice the base level [34]. Neural inhibitor effects of both adenosine and PGD2, have been recorded when they are artificially administered into the brain of test animals and, even in this case, the effect of these substances was not analgesic but just sedative [35]. The anesthetic effect of pregnanolone is observed only if injected in high doses, attaining high blood concentrations (2-2,5 μg/ml) [36].

Brain electrical activity is still rudimentary in immature fetuses: the

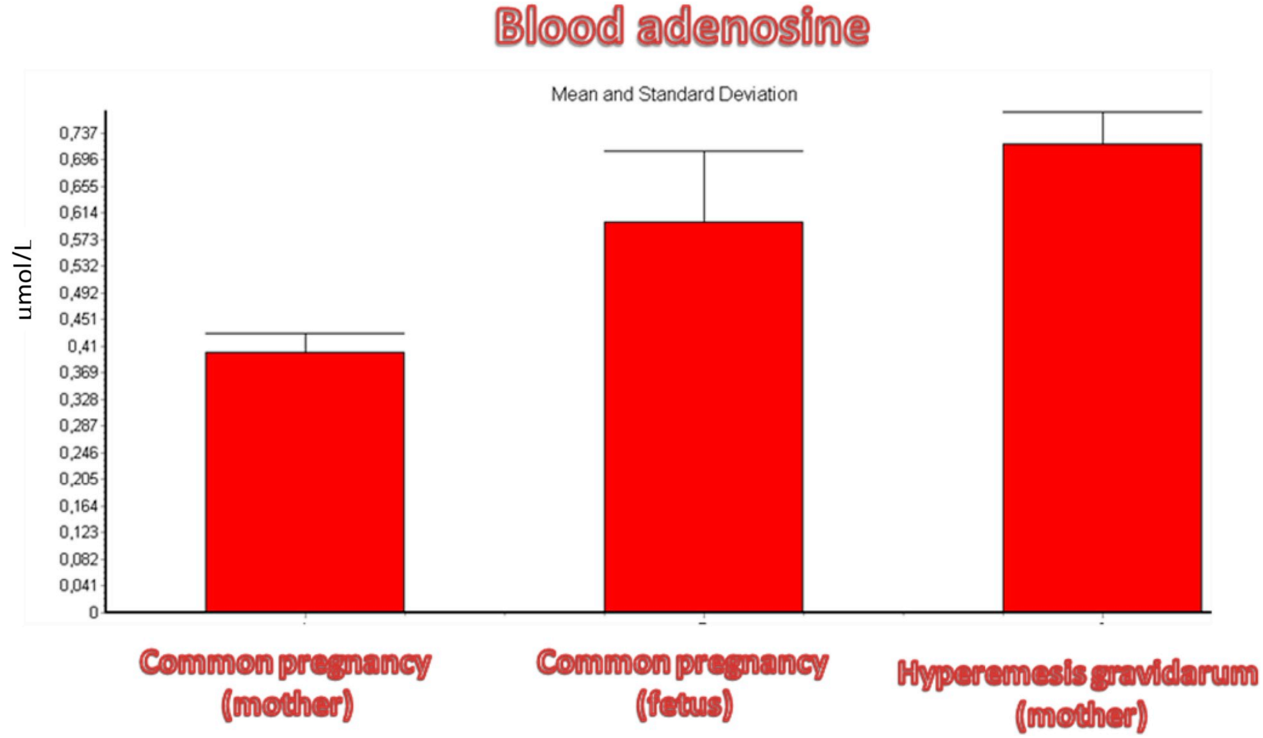

Fig. 1. Data are obtained from reference #30 and #31.

first signs of cortical EEG activity are recorded in prematurely born fetuses at 23 WGA, showing very long flat unreactive periods, interrupted by very high voltage bursts, with no sign of behavioral states. Anyway, fetal magnetoencephalography gives positive responses from 27 WGA [37], and fetal brain activation to sounds has been demonstrated using functional magnetic resonance imaging in fetuses of 33 WGA [38]. Using the information we have from premature babies, we know that at 26–28 weeks GA, evoked potentials may be recorded from somatosensory, visual, auditory and frontal cortex [39]. Near infrared spectroscopy in preterm infants has demonstrated localized somatosensory cortical responses from 24 weeks, following painful heel lance and venepuncture [40]. More recently, EEG has demonstrated evident nociceptive-evoked potentials in newborns of 35–39 postmenstrual weeks following heel lance [41].

An increase in stress hormones is seen after a painful intervention in 16–25 WGA fetuses: in a group of fetuses, an in utero blood transfusion was performed using the intrahepatic vein the process of which activates nociceptors, while a control group received the transfusion using the umbilical vein without activating the nociceptors [42]; the result was that in the former group, a dramatic increase of cortisol, adrenalin and beta-endorphines was seen, while in the latter, these hormones showed no changes in their blood level. In another study [43], the same procedure of intrahepatic transfusion was performed, but with prior administration of fentanyl to the fetus: the result was that the increase of stress hormones was much lower, compared with that of the first experiment.

1.3. Fetal pain and fetal surgery

Fetal pain and fetal surgery are highly correlated, because if a fetus can feel pain after a certain gestational age, then providing appropriate analgesia is important for three main reasons: medical ethics, the risk of long-term consequences of pain on the development of the brain and the possibility of sudden movements induced by pain that can jeopardize the surgeon's work [44].

Some researchers recommend administering 20 μg/kg of intramuscular fentanyl to the fetus prior to the procedure [45], while others recommend the administration to the mother of a continuous infusion rate of remifentanil 0.1 μg kg − 1 min − 1, to achieve fetal immobilization and maternal sedation, though they do not exclude directly administering analgesics to the fetus [46]. Some researchers utilized intra-amniotic opioids for fetal analgesia on lamb fetuses [47]: they showed that greater plasma concentrations were obtained in the fetal lamb as compared with the ewe, suggesting that this route might be utilizable for humans. In several studies, surgeons have directly administered opioids to the fetus, while others have considered maternally administered analgesics to be sufficient. A review of the literature to assess the state of the art of fetal analgesia during surgery retrieved 34 papers [48]. In three papers, surgery did not hurt the fetus, being performed on fetal placenta; in two papers, it was performed in the first half of pregnancy, when pain perception is unlikely and therefore analgesia is unnecessary. In 10 of the 29 remaining papers, fetal surgery was performed using direct fetal analgesia, while in 19, analgesia was administered only to the mother. In most cases, fetal direct analgesia was obtained using intramuscular. opioids, and muscle relaxant. Adverse effects on either fetuses or mothers due to fetal analgesia were rarely reported [49]. Recently it has been showed that fetuses during fetal surgery can respond to pain with bradycardia [50]; nonetheless, more research is needed to find out actual fetal pain markers. However, the anesthetic that pregnant women receive is not enough to anesthetize the fetus; in fact, fetuses born through cesarean section performed with maternal general anesthesia are born awake. Administering opioids and not only neuromuscular blockers to the fetus is also necessary because maternal laparocentesis, necessary to perform fetal surgery, does not necessarily require general maternal analgesia, but only local spinal analgesia.

2. Discussion

As we stated at the beginning of this review, determining if a fetus can feel pain is an important challenge, with two major limitations: the fetus cannot speak and we have no specific markers of pain, but only marker which measure both pain and stress. Anyway, if we rely on the hints and indications given by scientific observation, we can draw a series of ‘pros and cons’ about fetal pain. We report them in Table 1. It emerges from this review that pain, a progressive adaptive process that includes sensations and reactions, progressively appears throughout fetal life [51]. This may be due to the fact that in early stages of development, mammals do not have the need todefend themselves from external threats. To clearly understand when pain appears in a fetus, we should understand the sense of pain. It is a potent process aimed to make the organism react to threats recalling all its forces, and aimed to send a unambiguous alarm and a dramatic request for external help. Thus, it is why, from an evolutionistic point of view, it appears when life can be saved by use of these forces and by the external helps that cries summon, namely when the organism is mature enough. This interestingly corresponds to the observations reported in this text, that describe pain as a phenomenon that emerges in the middle of gestation – when a fetus acquires the possibility of surviving outside the womb, and that becomes more and more evident and significant with increasing gestational age. We report in Fig. 2 the most relevant steps in the development of the prenatal nociceptive system.

One frequently raised objection is that, since the fetus seems constantly in a sleep state, it cannot feel pain. This is contradicted by several observations we have reported: the fetus is not constantly in a sleep state, and above all, it can be awakened by external stimuli. Moreover, the substances that are supposed to shield it from pain, the neuroinhibitors, are at a level in the fetus' blood non significantly different from that in the pregnant mother's blood (allopregnenolone), or from that of pregnant mothers in particular states such as preeclampsia or hyperemesis gravidarum (adenosine an progesterone), while mothers are not anesthetized by these substances at these levels. Only pregnanolone is significantly higher in fetuses than in mothers, though its isomers do not differ in either. Anyway, neuroinhibitors are not anesthetics, but sedatives, and no sedation can eliminate or prevent pain. One evidence of fetal non-sedation is birth: all fetuses cry at birth, if they were anesthetized or deeply sedated, this would not be possible.

In conclusion, we should acknowledge that pain in infants was a debated matter until the end of the last century, and this exposed thousands of babies to untreated pain. Nowadays no physician is permitted to expose babies to a potentially painful treatment without providing due analgesia; but denying pain in foetuses would jeopardize these advances in care, because it would question the use of analgesia in neonates of similar WGA. Another negative consequence of denying fetal pain is that fetuses who go through surgery may not receive anesthetics, with the possible negative consequences we reported in the text. Nonetheless, the advances in this field are ongoing and we believe that, in the future, pain scales will be developed and validated for fetal pain, drugs will be refined to overcome it, and fetal analgesic treatments will eventually be available.

Table 1
Pros and cons for the likelihood of pain in the second half of pregnancy.

CONS	PROS
Immature cortex	Presence of thalamus and subplate
Scarce myelination	Adequate nociceptive pathways
Continuous sleep state	Periods of wake
Presence of neuroinhibitors	Arousability
Fetal non-verbality	Hormonal and behavioral signs of pain

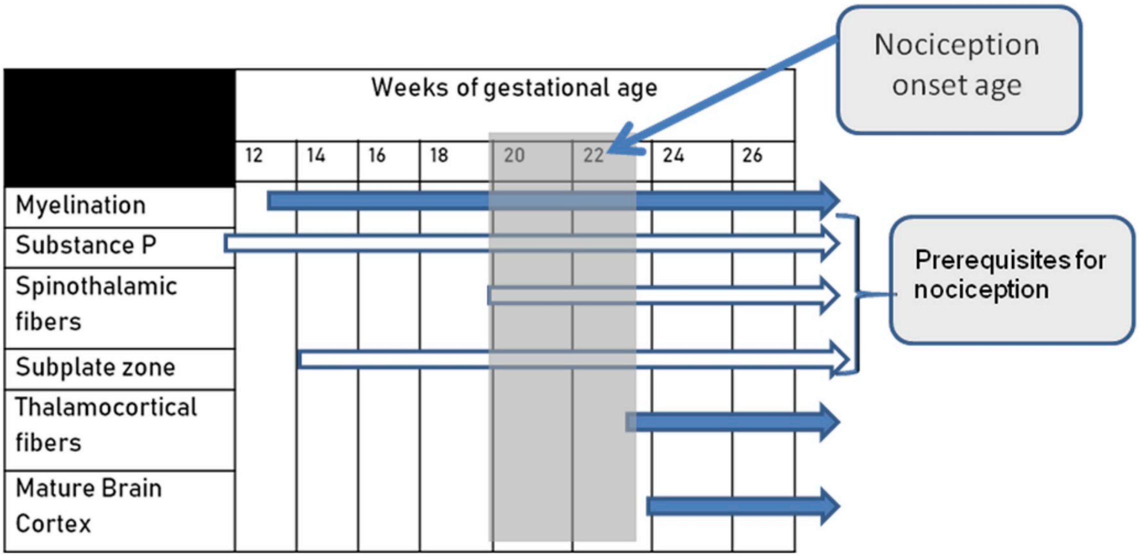

Fig. 2. The onset of nociception. The structures actually necessary for nociception are indicated by white arrows. The most likely age for fetal nociception onset is 20–22 weeks of postnatal age.

Conflicts of interest

I declare no conflict of interests.

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Nociception and the neonatal brain

Deniz Gursul, Caroline Hartley, Rebeccah Slater[*]

Department of Paediatrics, University of Oxford, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, United Kingdom

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ABSTRACT

Measuring brain activity in infants provides an objective surrogate approach with which to infer pain perception following noxious events. Here we discuss different approaches which can be used to measure noxious-evoked brain activity, and discuss how these measures can be used to assess the analgesic efficacy of pharmacological and non-pharmacological interventions. We review factors that can modulate noxious-evoked brain activity, which may impact infant pain experience, including gestational age, sex, prior pain, stress, and illness.

1. Introduction

In adults, self-report of pain is the gold standard of pain reporting, and correlates strongly with pain-induced brain activity [1]. Given that the cortex is where nociceptive inputs are modulated and influenced to form subjective pain experiences [2], it follows that non-invasive brain imaging may provide the closest estimate of pain perception in the absence of a verbal report. This is of key utility in non-verbal neonates who cannot communicate their pain perception verbally, as alternative surrogate measures, such as facial grimacing, motor responses and autonomic activity, may not be as reliably linked to the perceptual experience, and may be more highly influenced by contextual factors [3].

Providing analgesia for infants is crucial, as pain in early life can cause negative short-term and long-term consequences. Short-term effects include decreased physiological stability, such as increased heart rate [4] and decreased respiration rate [5], and long-term effects include altered pain thresholds [6–9], and neurocognitive development, including alterations in brain structure, behaviour, and cognitive ability [10–12]. These differences have been reported to be present in school-age children, and continued research is now beginning to report differences persisting into adulthood [13].

Infant pharmacokinetics and pharmacodynamics differ from those of adults [14], and providing analgesia to infants is not straightforward as it cannot be assumed that the analgesics that work in adults are efficacious or safe in infants [15]. Noxious-evoked brain activity is modulated by analgesics in both adults [16–20] and infants [21]. Therefore, brain imaging can potentially provide an objective and specific method of estimating infant pain experience and analgesic efficacy, and is of valuable utility to aid the discovery of effective analgesics [22]. Information on analgesic efficacy can then be used to determine whether the benefits of the intervention outweigh any potential adverse side effects [23].

In this review, we detail the different methods by which it is possible to measure pain-related brain activity in infants, and how these methods can be used to assess the efficacy of analgesics and non-pharmacological interventions. Additionally, we discuss the factors affecting the measurement of noxious-evoked brain activity and the assessment of infant pain.

2. Methods of pain assessment

2.1. Brain imaging

2.1.1. NIRS (Near-infrared spectroscopy)

NIRS measures changes in cerebral oxygenation to infer functional brain activity, relying on the assumption that increased tissue oxygenation reflects an increase in blood flow due to increased neural

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[*] Corresponding author. University of Oxford, Medical Sciences Divisional Office, Level 3, John Radcliffe Hospital, Oxford, OX3 9DU, United Kingdom.
E-mail address: rebeccah.slater@paediatrics.ox.ac.uk (R. Slater).

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activity. NIRS has been used in both adults [24] and infants to look at sensory evoked activity [25,26]. Due to its portability and ease of application, NIRS was the first measure of brain activity used to investigate whether afferent nociceptive input was transmitted to the infant cortex. This demonstration that noxious-evoked activity could be transmitted to the infant cortex – which is necessary for the experience of pain – was an important step forward in infant pain research. An optical sensor was placed on the scalp over the somatosensory cortex, which is located superficially and therefore more accessible to non-invasive optical techniques such as NIRS [27], and increased cerebral oxygenation was observed after clinically necessary noxious stimuli (heel lance blood tests and venipuncture), but not after non-noxious control stimuli [28,29].

NIRS has since been used to measure brain activity evoked by heel lances in independent samples of infants [30,31] and to other clinically necessary procedures, such as chest drain removal [32]. These studies have added further evidence to support the claim that the NIRS signals being measured reflect noxious-evoked haemodynamic changes in brain activity, and have demonstrated that pain-related NIRS signals can be observed in sedated infants despite dampened pain behaviours, highlighting that measures of brain activity may provide additional information about the infant pain experience. However, a limitation of NIRS is that the observed signals are based on the assumption that there is a direct correspondence between the increased blood flow and underlying brain activity, although this relationship may be influenced by many factors [33] and is more complex in the developing immature brain.

2.1.2. EEG (electroencephalography)

EEG records the electrical activity of neural populations with an array of electrodes on the scalp and is also portable, but allows for a higher temporal resolution than NIRS. EEG has been used to record event-related potentials in both adults [20,34,35] and infants [36,37] following a range of stimuli, and EEG application is not associated with increased stress levels in infants [38].

In 2010, Slater et al. identified a noxious-evoked potential in infants, which occurs at ~500 ms after a heel lance blood test over the vertex of the scalp [39] and is evident in single trials. This potential is also observed following low intensity experimental noxious stimulation, is graded with the intensity of the noxious stimulus [40], and is not observed following auditory, visual, or non-noxious tactile stimuli [21]. A similar pattern of noxious-evoked brain activity has also been recorded following vaccinations in infants aged 1 month to 1 year [41], demonstrating the commonality of this response following different noxious stimuli and in older age groups.

In order to use this evoked potential as an objective measure in clinical trials of analgesics it needs to be validated in independent samples of infants. A template of noxious-evoked brain activity [21] was derived from the brain activity of a sample of term infants following heel lance blood tests and experimental noxious stimuli, and then validated in four independent studies. Given a new EEG trace, this template can be projected onto the data and is essentially scaled to best fit the noxious-evoked response, providing a useful objective and automated method for quantifying the magnitude of infant noxious-evoked brain activity. In one validation study, the magnitude of the noxious-evoked brain activity quantified using the template was modulated by local anaesthetic, demonstrating its utility to objectively test analgesic efficacy. The reproducibility of this method has been demonstrated, with researchers from independent institutions recording noxious-evoked brain activity that can be reliably fitted with this template [42].

A limitation of this method is that measuring evoked activity at one location on the scalp does not reflect the full extent of nociceptive processing across the brain, and so analysis across a wider spatial area could improve our understanding and measurement of pain-related brain activity. Furthermore, the template can only be used to quantify noxious-evoked activity following acute, previously-characterised procedures. As many clinically relevant procedures occur instead over minutes or even hours, a different measure, such as changes in the EEG frequency, may be more suitable to characterise pain-related brain activity. Numerous studies have utilised EEG to characterise changes in the frequency domain of brain activity in adults, following both acute and sustained noxious stimulation (including intramuscular injections, thermal and laser stimulation), with observed changes in the alpha, beta, gamma, and delta bands [43–47]. Alpha power has been suggested to be predictive of subjective pain perception [48,49] and Misra et al. [50] utilised a machine learning approach to show that pain perception can be classified based on pain-related changes in the power of EEG bands, demonstrating that there are characterisable and specific pain-related changes in EEG power which could be used to create a signature to identify pain. An increase in gamma oscillations, consistent with the adult response, has been observed following heel lance in infants [51]. Further characterization of changes in the time-frequency domain in relation to different noxious stimuli may provide a surrogate marker of the ongoing pain experience in infants.

2.1.3. fMRI (functional magnetic resonance imaging)

fMRI measures changes in blood oxygenation to infer changes in brain activity, commonly using a technique called blood oxygenation level dependent (BOLD) imaging. Changes in the BOLD signal can be localised with high spatial resolution, enabling the identification of anatomical brain areas that are active during particular states. In adults, brain regions that are active during reported pain have been identified, including the primary somatosensory cortex, prefrontal cortex, anterior cingulate cortex, thalamus, insula, and amygdala [2,52]. A neurological signature of pain, which can discriminate between pain and non-pain states, has been identified in adults and it has been suggested that such a signature would be useful in non-verbal populations [17,53,54]. The feasibility of scanning neonates in response to noxious stimulation has been established [55] and the methods for both acquisition and analysis have been optimised, including design of neonatal specific head coils [56], optimization of echo time [57], identification of the infant haemodynamic response function [58] and development of bespoke analysis pipelines [59]. The regions of the infant brain that are active following experimental noxious stimulation have been identified [60,61] and closely resemble those active during the adult experience of pain, including both sensory and affective brain regions.

Development of an fMRI-based signature of pain-related brain activity in infants would provide an objective approach to investigating which aspects of pain-related brain activity are modulated by interventions. Adult studies have suggested that fMRI could be used to optimise central nervous system (CNS) drug development in early-stage clinical trials, by providing insight into how drugs affect the brain in order to identify and prioritize the development of more promising candidates [18,62,63]. In the future, application of such a method could be of use in infants, in whom an objective method of drug testing and drug development is even more critical due to their lack of ability to verbally communicate their pain perception.

2.2. Electromyography (EMG)

EMG involves the placement of electrodes on the skin overlying muscle to quantify muscle activity. In the field of pain, EMG is applied to limbs to measure reflexes, which occur in both adults and infants in response to noxious stimulation in order to protect the body by minimizing contact with potential harm. Infant reflexes exhibit intensity encoding, correlating with the intensity of the noxious stimulus eliciting the reflex [64]. Although the magnitude of the reflexes elicited by noxious stimuli correlate with noxious-evoked brain activity [40], reflexes, especially in younger gestational age infants, also occur in response to tactile stimulation [65], meaning that they are not as specific a reflection of noxious input as noxious-evoked brain activity.

2.3. Behavioural and physiological measures

Behavioural and physiological surrogate measures of infant pain are the most common measures used for clinical pain assessment. Factors such as facial expressions (including brow bulge, nasolabial furrow, eye squeeze, facial muscle tension, and grimace), limb and torso movements, cry, heart rate, and oxygen saturations are measured in order to estimate infant pain levels. There are many composite measures of pain, including the Premature Infant Pain Profile-Revised (PIPP-R) [66], Neonatal Infant Pain Score (NIPS) [67], Behavioural Indicators of Infant Pain (BIIP) [68], Echelle Douleur Inconfort Nouveau-Ne (EDIN) [69] and the COMFORT scale [70], and these take into account a range of behavioural and physiological variables to provide a better estimate of infant pain. However, neonatal staff report difficulty with assessing pain based on behavioural and physiological indicators [71], and behavioural and physiological measures may also reflect other emotions such as distress [72,73]. Investigating how these measures relate to noxious-evoked brain activity across different infant populations (including those with illness or cerebral pathology) may improve our understanding of these behavioural responses.

2.4. A multimodal approach to pain assessment

It is clear that pain elicits a range of responses across the infant central nervous system that can be reliably recorded. These different measures of pain-related brain activity are often concordant. For example, group-level measures of brain activity recorded by NIRS and EEG demonstrate correlation [31], and EEG-recorded noxious-evoked brain activity correlates with both reflex withdrawal [40] and facial expression changes [21,74]. However, this is not always the case – some individuals do not have correlated NIRS and EEG responses [31], noxious-evoked brain activity can be observed in the absence of facial expression responses[[21,40,75]], behavioural and physiological measures are not always harmonious [76,77], and cry presence or amplitude does not correlate with noxious-evoked brain activity [78,79]. Additionally, contextual factors and interventions can disrupt the relationship between ordinarily concordant measures: stress [80] and prior pain [81] disturb the relationship between behavioural measures and noxious-evoked brain activity, sucrose reduces facial expression responses but does not alter noxious-evoked brain activity or reflex withdrawal [82], and gentle touch reduces noxious-evoked brain activity but does not appear to alter reflex withdrawal [83].

These disassociations could be due to a range of reasons, including low signal to noise ratios when necessarily considering single trial responses, the distinction between distress and pain, and the immaturity of the developing cortical and corticospinal connections [84,85]. The discrepancies between these measures highlight how pain-related activity at different sites across the body reflect different aspects of the pain experience. Furthermore, it demonstrates how these patterns of activity can be independently modulated by comfort measures, the environment, or prior experience. These observations emphasize the importance of considering a comprehensive multimodal approach to pain assessment to allow the best estimation of the infant pain. A multimodal approach to pain assessment is well suited to answering research questions and may be particularly important when considering analgesic drug trials. A carefully considered multimodal approach to analgesic assessment, including brain imaging as well as physiological and behavioural indicators, is most likely best able to detect potential adverse side effects of potential analgesics as well as assess efficacy [15].

3. Use of brain imaging to assess potential pharmacological and non-pharmacological interventions

Given the adverse short-term and long-term effects of pain [4–13], and also the potential negative side effects of analgesics, more information on both drug efficacy and drug safety in infants is needed to balance analgesic efficacy with potential adverse drug effects [23]. Previous clinical trials using behavioural and physiological indicators of pain as study endpoints have not always provided clear answers regarding the efficacy of potential analgesics [22,86–88]. In this section, we discuss how the different methods of brain imaging could be used to better assess the efficacy of pharmacological and non-pharmacological methods of pain relief.

3.1. Sucrose

Oral sucrose and similar sugar solutions are commonly given to infants as a method of pain relief [89], and many studies demonstrate reduced pain-related behaviour and physiology associated with oral sucrose administration [90]. NIRS was the first method of brain imaging used to investigate the effect of sucrose on brain activity following heel lancing [91] with no significant difference reported in cerebral blood volume between the sucrose or placebo group, despite reduced heart rate and crying after sucrose administration. In agreement with this study, Beken et al. [92] investigated infant brain activity following venipuncture, and found that dextrose caused greater changes in cerebral blood volume in the left frontoparietal region of the brain, but did not alter cerebral blood flow or tissue oxygenation when compared with sterile water administration, despite dextrose-associated reduced behavioural scores. Due to its location, the increase in frontoparietal blood volume was interpreted as an effect of the sugar solution on the brain but not on pain processing, and it was concluded that dextrose did not alter pain-related brain activity.

However, Bembich et al. have also used NIRS to investigate the analgesic efficacy of glucose, as well as breastfeeding, in two studies suggesting that both do alter pain-related brain activity [93,94]. In the first study, oral glucose was found to block or weaken cortical activity following heel lancing, whereas breastfed infants showed widespread cortical activation but presented significantly less behavioural pain expressions. In the second study, the effect of maternal relationship was investigated, with infants being held during sucrose administration or breastfed (rather than fed expressed breastmilk) benefiting from the greatest analgesic effect.

Similarly, EEG recordings have also been used to investigate the effect of sucrose on noxious-evoked brain activity. Fernandez et al. [95] reported that sucrose attenuated a right frontal increase in EEG activation after heel lancing. In contrast, in 2010 Slater et al. [82] found that sucrose did not affect the magnitude of noxious-evoked brain activity, despite reducing pain-related behaviour concordant with previous investigations [90]. It is likely that the noxious-evoked brain activity quantified by Slater et al. provides a more specific measure of the nociceptive activity as compared with either the NIRS studies or the EEG spectral frequency changes considered by Fernandez and colleagues as the study by Slater and colleagues compared the evoked activity with a control stimulus and analysed only the noxious-specific component of the response. It seems likely that sucrose may reduce distress-related behaviour and physiology but not alter noxious-specific processing, which means it also may not protect against the long-term adverse consequences associated with early life pain and its effects on the brain [96]. Additionally, the benefits of sucrose use as a comfort method in infants needs to be carefully balanced with possible negative side effects in light of research suggesting that repeated sucrose administration leads to altered brain structure in animal models [97] and altered neurobehavioural development in 40 week old infants [98]. Further research remains to be done to determine the long-term effects of sucrose use in humans.

3.2. Topical local anaesthetic

The current literature, which has relied on behavioural and physiological measures of infant pain, is divided on the analgesic efficacy of topical local anaesthetic (LA) in infants, with some studies concluding that LA is effective for a range of acute needle-related procedures such as heel lances, cannulation, and venipuncture, and others concluding that it is not [87]. Noxious-evoked brain activity following experimental noxious stimuli is reduced by LA [21], demonstrating that LA is effective in blocking peripheral nociceptive input. The lack of observed pain relief in earlier studies could be due to factors such as the choice of LA, length of application time, the limited penetration depth relative to the noxious stimulus, or due to the non-specific behavioural and physiological measures used to assess analgesic efficacy: infants may cry and exhibit facial expressions and increased heart rate due to the general distress associated with clinical procedures (for example, from having their hand held firmly in position for cannulation), regardless of the level of pain they are perceiving [21,22]. However, further work is needed to investigate whether noxious-evoked brain activity following clinical stimuli, which have a deeper penetration and are higher intensity, is also reduced.

3.3. *Morphine*

As with local anaesthetic, the literature has not yielded conclusive results regarding the analgesic efficacy of morphine in infants [86], with some studies reporting that morphine does provide adequate analgesia [99–101], and others concluding that it is not an effective form of pain relief [102,103]. The Poppi (Procedural Pain in Premature Infants) trial, a blinded, randomised, placebo-controlled trial [15,104], aimed to investigate whether oral morphine was an efficacious and safe analgesic for procedural pain in non-ventilated premature infants and used a multimodal approach, including measuring brain activity, behaviour, physiology, and reflex withdrawal to assess the responses to heel lancing and Retinopathy of Prematurity (ROP) eye screening. The trial was stopped early due to profound respiratory side effects. Morphine did not alter the magnitude of noxious-evoked brain activity following heel lancing, nor did it alter the PIPP-R [66] behavioural scores to either heel lancing or ROP screening, though the trial was underpowered due to early cessation and it was therefore not possible to draw conclusions about the analgesic efficacy of morphine. Importantly this trial demonstrates the importance of taking a multimodal approach to analgesic assessment, including the thorough analysis of potential adverse effects and the utility of brain imaging. The trial concluded that oral morphine at a dose of 100 μg/kg should not be recommended for non-ventilated infants for ROP screening due to its risk of adverse effects.

3.4. *Skin-to-skin contact*

Skin-to-skin contact is a comfort measure which reduces behavioural and physiological measures of infant pain [105]. NIRS has been used to investigate the effect of skin-to-skin contract on brain activity in preterm neonates undergoing venipuncture [106]. A significantly smaller increase in oxygenated haemoglobin was found when the infants were being held by their mothers compared with when they were lying in their cot or incubator, consistent with a lower behavioural and physiology pain-related score. The authors concluded that skin-to-skin contact had a pain-relieving effect.

3.5. *Slow touch targeted towards C-tactile fibres*

Slow, gentle touch at a velocity of approximately 1–10 cm/s has been demonstrated to reduce both self-reports of pain and pain-related brain activity in adults [107,108]. This effect is believed to be mediated by C-tactile (CT) fibres, a subclass of mechanoreceptor in the skin which respond to the pleasant aspects of touch [109,110], encouraging affiliative behaviours [19]. In infants, gentle massage has been shown to reduce pain-related behaviours and physiology [111–115]. This may be related to activation of CT-fibres; noxious-evoked brain activity in term infants (in response to both experimental noxious stimulation and clinically required heel lance) is reduced by slow gentle brushing [83], performed at a rate known to activate CT-fibres in adults [110]. As pain relief interventions are limited in infants and non-pharmacological methods of pain relief do not hold the risk of adverse side effects, evaluating their efficacy is essential. Determining whether gentle touch also modulates noxious-evoked brain activity in preterm infants will be an important next step.

4. Factors affecting noxious-evoked brain activity and the measurement of infant pain

Many factors influence how an infant responds to noxious stimulation, including their gestational age, sex, prior pain exposure, illness, and stress levels. Here we describe how noxious-evoked brain activity may be influenced by some infant contextual factors and how this changes in relation to other pain-related responses.

4.1. *Gestational age and sex*

Noxious-evoked brain activity measured with both EEG and NIRS increases in magnitude and decreases in latency during preterm development [28,116]. Noxious-specific potentials measured with EEG are more likely to occur in older infants, maturing from the non-modality specific burst patterns of EEG, known as delta brushes, seen in infants below ∼34–37 weeks gestational age[[116,117]]. In term infants, functional connectivity (measured with fMRI) between regions in the descending pain modulatory system (DPMS) has been associated with lower noxious-evoked brain activity, suggesting that the DPMS has an inhibitory influence on noxious responses from a young age and that the development of the DPMS during early infancy will influence the magnitude of observed noxious-evoked brain activity [61].

Reflexes also mature during the preterm period, decreasing in magnitude, duration and latency, increasing in activation threshold, and beginning to occur more discriminately after solely noxious events rather than also tactile stimulation [64,65,116]. This refinement is concomitant with an increase in the magnitude of noxious-evoked brain activity, suggesting that top-down modulation of reflexes may begin to emerge in early postnatal life, consistent with animal studies[[84,85,116]]. However, a dissociation between noxious-evoked brain activity and reflex withdrawal has been observed following the application of CT-optimal touch in term infants [83], which reduced brain activity but not reflex withdrawal. This may be due to immature descending corticospinal tracts limiting communication between the brain and spinal cord [84,85] and suggests that top-down inhibition is not fully mature at term age.

Facial expressions similarly change with age: the latency to facial expression change decreases with postmenstrual age [118], the duration of brow bulge, eye squeeze, and nasolabial furrow in the 30 s post stimulus increases with age, and infants are more likely to exhibit a discriminate facial response (to noxious stimuli but not non-noxious touch stimuli) over ∼ 33 weeks gestational age, concomitant with the maturation of noxious-specific brain activity [74]. Some behavioural and physiological measures of infant pain, such as the PIPP-R [66] and EDIN6 scale [119], account for gestational age in their points systems, allowing for the fact that younger infants are less likely to respond.

Sex-dependent differences in brain activity responses to noxious stimuli have been observed using EEG [120], with female infants more likely to exhibit widespread rather than localised pain-related potentials. Several behavioural studies have also reported sex-dependent differences, with female infants displaying more pain-related facial features [121] and higher pitch crying [122] than male infants. In concordance with this, the adult literature also reports differences in male and female pain perception, and the intensity and spatial distribution of pain responses [123].

4.2. Stress, illness and prior pain

Infants who are under stress or sick display differing responses to noxious stimuli. Jones et al. [80] found that stress (measured utilising salivary cortisol samples) leads to a dissociation between noxious-evoked brain activity and noxious-evoked behaviour, measures of pain which are usually correlated, with an increase in noxious-evoked brain activity but not behaviour. This is consistent with adult evidence that stress enhances pain sensitivity [125], but could lead to inaccurate estimations of infant pain based on behavioural indicators - further demonstrating the importance of a multimodal approach to infant pain measurement.

Illness also affects measurements of pain, with extremely sick infants less able to mount facial or behavioural responses [27] and displaying altered cry acoustics [126]. Additionally, behavioural measures can be difficult to observe in instances where clinical equipment such as intubation is present and masking facial features or the ability to cry [127]. Future research is required to investigate noxious-evoked brain activity in these infants, shedding light on their pain experience.

Regarding prior pain, Slater et al. [6] used EEG to determine that noxious-evoked potentials following clinically necessary heel lances were larger in ex-premature infants at term-corrected age (having spent time in neonatal units undergoing painful procedures) than in age-matched term-born infants. Ozawa et al. [81] demonstrated that prior pain disrupts the relationship between cortical and behavioural measures of pain, indicating that prior experiences should be taken into account when assessing neonatal pain. Prior pain also influences behavioural pain scores in both premature infants [128] and term-born infants [129]. Moreover, these effects may continue into childhood and adulthood: children who have experienced early life pain display increased cerebral responses to pain [130] and pain catastrophising [131], and early life surgery is related to altered somatosensory processing in young adults [13].

5. Conclusion

Measures of noxious-evoked brain activity are a useful tool for infant pain assessment as they are objective and quantifiable, and changes in brain activity are likely to be related to the experience of pain. These features mean that brain activity is also well suited for investigating analgesic efficacy. Noxious-evoked brain activity is generally correlated with other indicators of infant pain, however, brain activity can be seen in the absence of these indicators, and is influenced by contextual factors such as infant age, sex, prior pain, stress levels, and illness. A multimodal approach to pain assessment, including the measurement of noxious-evoked brain activity, can provide the most comprehensive estimate of the infant pain experience.

Conflicts of interest

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Practice points

- Neonatal staff should be aware that noxious-evoked changes in brain activity can be recorded in infants even when there are no visible pain-related behaviours.
- Neonatal staff should be aware that interventions (such as oral sucrose) may dampen pain-related behaviours without affecting noxious-evoked brain activity.
- Neonatal staff should be aware that contextual factors such as age, sex, prior pain, stress, and illness will influence how an infant responds to noxious input, and that these factors can disrupt the relationship between different measures of noxious-evoked activity.

Research directions

- Noxious-evoked changes in brain activity should be characterised following longer clinical procedures and post-operative pain.
- Different modalities of brain imaging should be developed to provide well-defined templates of noxious-evoked brain activity.
- Brain imaging should be included with other pain assessment measures in clinical trials that aim to assess the efficacy of analgesic interventions.

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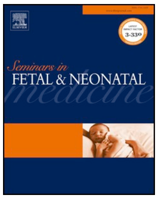

Non-invasive monitoring of stress biomarkers in the newborn period

C. Peña-Bautista[a], R. Escrig[b], I. Lara[b], A. García-Blanco[a], C. Cháfer-Pericás[a,*], M. Vento[a,b,**]

[a] *Neonatal Research Unit, Health Research Institute La Fe, Valencia, Spain*
[b] *Division of Neonatology, University and Polytechnic Hospital La Fe, Valencia, Spain*

ABSTRACT

The neonatal period is a highly sensitive time span during which stressful experiences may have an influence on later health outcomes. Medical procedures applied to newborn babies during hospitalization are stressors that trigger a physiological and psychological stress response. Stress response has been traditionally evaluated using scores based on behavioural signs such as facial expressions, limb movements, crying, etc., which are subjectively interpreted. Only few studies have employed measurable physiological signs to objectively evaluate the stress response to specific interventions.

The aim of this review is to inform of recently developed biochemical methods that allow clinicians to evaluate the stress response to medical procedures performed in the neonatal period in biological samples non-invasively obtained. Stress biomarkers are based on the physiological stress response mediated by the hypophysis-pituitary-adrenal axis and the sympathetic-adreno-medullary systems. Cortisol is at present the most widely employed laboratory determination to measure stress levels. In recent years, sequentially determined salivary cortisol levels have allowed non-invasive monitoring of newborn infants under stressful conditions in the NICU.

1. Introduction

Stress was first defined by Hans Selye as *"the non-specific response of the body to any demand for change"* [1]. From a biological point of view, it could be interpreted as the unspecific physiological response to certain triggering factors (internal or external stressful stimuli) that imply an activation of endocrinological systems [2]. These neuroendocrine systems include the hypothalamic-pituitary-adrenal (HPA) axis and the efferent systemic sympathetic-adreno-medullary systems (SAM) [2]. The most studied stress biomarkers are cortisol as indicator of HPA axis activity [3] and α-amylase as indicator of Sympathetic-Adreno-Medullary (SAM) axis activity due to its association with catecholamines [4]. Importantly, when stress stimuli are prolonged or very intense, the stress response may adversely affect crucial physiological functions such as growth, metabolism, circulation, immune response, etc. [2].

Assessing the stress response in newborns is difficult. It has been approached from different perspectives such as measurement of clinical variables (e.g.: heart rate, blood pressure, sweating response, etc.), or specifically designed scoring systems based on the interpretation of behavioral response (facial expressions, limb movements, crying, etc.). However, all these methods frequently lack reproducibility, are interfered with by other physiopathological circumstances or are excessively subjective [3]. In recent years, determinations of cortisol and α-amylase in biofluids such as amniotic fluid, plasma, and saliva have been broadly employed to determine the level of stress under specific circumstances or medical interventions [5]. In the newborn period, the tendency is to avoid using invasive methods for research purposes. Under these circumstances, both urinary and saliva analytical methods to reliably determine stress biomarkers have been validated and increasingly employed [6].

Accumulated evidence has shown that repeated stressful input during a sensible period such as the neonatal period may have profound and long-lasting effects upon brain development [7]. Survival of preterm infants has significantly increased in the last decade [8]; however, this is at the expense of being subjected to by a multitude of stressors that act during a period of extreme vulnerability upon the central nervous system and may lead to unwanted consequences [9].

This review article describes the physiology of the stress response and underscores its importance in the neonatal period. Moreover, clinical scoring systems employed to measure pain-derived stress response and analytical methods employed to assess stress biomarkers using non-invasive matrices are described.

2. Physiology and pathophysiology of the stress response

2.1. Chronic dysregulation of the stress physiological system

The physiological systems involved in the stress response (Fig. 1) are constituted by: (i) central components represented by different neuronal types responsible for the secretion of corticotropin releasing

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[*] Corresponding author. Health Research Institute La Fe, Avenida de Fernando Abril Martorell, 106, 46026, Valencia, Spain.
[**] Corresponding author. Health Research Institute La Fe, Avenida de Fernando Abril Martorell, 106, 46026, Valencia, Spain.
E-mail address: m.consuelo.chafer@uv.es (C. Cháfer-Pericás).

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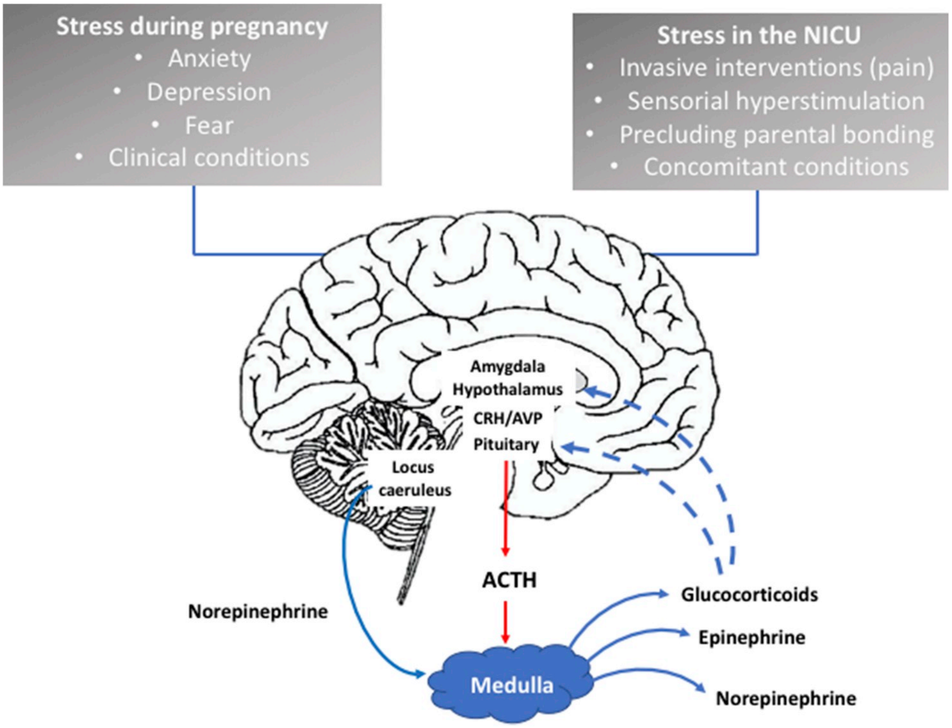

Fig. 1. Diagram representing the mechanisms involved in acute and chronic stress procedures.

hormone (CRH), arginine-vasopressin, or norepinephrine; and (iii) peripheral components represented by the HPA-axis, the efferent systemic SAM systems, and components dependent on the parasympathetic system [2]. The SAM axis is involved in preparing the body for sustained physical effort and decision making by means of the activation of the sympathetic branch of the Autonomic Nerve System in the brain, which in turn activates the adrenal medulla provoking the release of catecholamines that subsequently stimulate different target organs including brain and gastrointestinal tract among others [2] (Fig. 1). On the other hand, the HPA axis is involved in maintaining the parameters of effort and attention by means of the activation of the pituitary gland in the central nervous system which, in turn, activates the adrenal cortex leading to the release of glucocorticoids (GCs) into the systemic circulation (Fig. 1). GCs regulate the basal activity of the HPA axis. Of note, high plasma GCs concentrations act upon the hypothalamus and the pituitary gland forming negative feedback loops on the secretion of CRH and ACTH. GCs receptors that are widely distributed throughout the brain and peripheral tissues [10]. GCs control the resting and stress-related homeostasis, maintain the cardiovascular tone, regulate hepatic, muscular, and adipose tissue catabolism, and influence the inflammatory and immune responses. Moreover, GCs also influence other relevant functions such as reproduction, growth, behaviour, cognition, and electrolyte and water homeostasis [11]. In this sense, acute stress situations trigger a bundle of behavioural responses including alertness, increased arousal, improved cognition, focused attention among others [12]. In addition, physical adaptation to stress requires an increased oxygen supply to brain, myocardium, and the stressed body site, an increased cardiovascular tone and a shift towards catabolism to supply energy producing metabolites to the organs [13].

Repeated or very intense stress stimuli may have long-term somatic consequences. Chronic overproduction of cortisol and catecholamines lead to alterations in the secretion of insulin, growth, and sex steroid hormones [12]. The consequences are adiposity, sarcopenia, and osteoporosis and metabolic syndrome with carbohydrate intolerance, dyslipidemia, and arterial hypertension [12,14]. Moreover, chronic stress during this vulnerable period may impact growth and specific brain structures with life-long consequences on health [13]. Experimental studies have shown that chronic stress reduces the volume of the hippocampus, amygdala, and frontal cortex, brain structures involved in high-level reasoning process, decision-making process, reward processing, emotional regulation, and frustration tolerance. As a consequence, learning, memory, control of the stress system, and behavioural problems may arise [15].

2.2. *Stress and inflammation*

The association between the immune system and the SAM and HPA axis may explain the damage of stress on health. The SAM and HPA axis activate the immune system by means of the secretion of proinflammatory cytokines [16]. Specific proinflammatory cytokines such as interleukin 1 or tumour necrosis factor α, enhance the biological response to infection, inflammation, and trauma and even block the anti-inflammatory response contributing to fever, inflammation or even tissue destruction leading to shock, death or chronic conditions such as rheumatoid arthritis or inflammatory bowel disease among others [17]. Additionally, a prolonged secretion of proinflammatory cytokines contributes to neurotoxicity and neurodegeneration altering the noradrenergic, serotonergic and dopaminergic systems leading to impaired neurodevelopment [18–20].

2.3. *Pain and stress*

The HPA axis activation following an acute stress causes an elevation of CRH subsequently eliciting analgesic rather than pronociceptive effects [21]. Contrarily, chronic stress has been associated with allodynia and hyperalgesia. Rodents treated for long periods of time with cortisone exhibit intense pain reactions to cold, heat, or mechanical stimuli [22,23]. Moreover, further studies in rodents have also shown that increased HPA axis activation in response to early-life psychological stress may alter pain mechanisms in later life and elicit intense pain responses or compromised stress-induced analgesia even under acutely stressful conditions (for a review reference # [24]).

The central nervous system of newborn infants, and especially preterm infants is vulnerable to excitoxicity, oxidative stress, and inflammation. Hence, repeated exposure to neonatal pain-related stressful stimuli has been associated with altered brain microstructure and stress hormone levels, and neurodevelopment alterations which involve cognitive and motor disabilities such as behavioral problems [25].

3. The neonatal intensive care unit environment

3.1. Stress in the NICU

Undoubtedly, the NICU is a stressful environment for preterm infants. Survival of preterm infants with increasingly lower gestational ages entails prolonged NICU stays with the subsequent long-term exposure to stressful stimuli due to both medical procedures and the NICU environment. Firstly, hundreds of medical procedures are performed in such vulnerable infants as extremely low birth weight (ELBW) neonates in the first days after birth [26]. A substantial number of these interventions are highly stressful and can be perceived as painful such as heel pricks or vein, lumbar or thoracic punctures. Despite the introduction in recent years of protocols fostering the use of non-invasive procedures and the implementation of local and general analgesia and sedation, the amount of pain derived from stressful stimuli is still substantial [27]. In addition, other interventions such as clustered care, position changing, care of the airway, intravenous drug administration, etc., prompt stress responses in very preterm infants [28]. Invasive and non-invasive interventions trigger clinically-perceived responses in preterm infants such as tachycardia, hypotension, hypoxemia, hypothermia, or increased intracranial pressure, but also increases in stress hormones [29]. Finally, relevant aspects of the NICU environment which include sensorial hyperstimulation especially noise and light also provoke stress responses in the preterm infant [9]. The cumulative effect of the long-lasting stay in the NICU, submitted to stressful interventions/environment puts the ELBW infant at high risk of chronic stress with long-term consequences such as postnatal alterations in growth, neurobehavioral, cortical activation, and brain development outcomes [30,31].

3.2. Stressor scales for the newborn infant

In recent years, new protocols aiming to reduce stress in the NICU have been put forward. Interventions such as reducing noise and light, minimal and gentle care handling, prolonged periods of skin to skin contact, avoidance of invasive interventions with increased use of non-invasive ventilation, or point-of-care ultrasound have become standard of care. However, the use of effective interventions to reduce stress in the neonatal patient in the NICU requires reliable means of evaluating the level of stress as well as the efficacy of the intervention. In this regard, most of the clinical scores developed are based on clinical parameters that can be monitored (desaturations, tachycardia, hypotension) and evaluation scores based on behaviour such as the facial expressions (grimace), crying, agitation, alertness or muscle tone. However, these scales are highly dependent on the caregiver's knowledge of pain physiology, attitude towards pain and its expression, sensitivities to the patient, and attitudes or biases regarding pain [27]. Therefore, the Achilles heel of these assessments is an excessive individual-dependent scoring system. In addition, preterm infants' behavioral and physiological responses to stress stimuli are not always identifiable. Moreover, the stress response can be modulated by accumulated experiences, gestational age, and postconceptional age, gender, position and prenatal exposure to betamethasone among other factors [9]. Multimodal assessments usually employed combine both observable behavioral reactions and clinical autonomic indicators of stress responses. However, behavioral responses are subjectively biased [32] and the measurement of clinical autonomic indicators is usually carried out under patient sedation [27].

4. Non-invasive biochemical stress biomarkers

4.1. Cortisol under stressful situations

The physiological response to high stressful stimuli in newborns has been evaluated using different biomarkers [33,34]. At present, cortisol is the most employed biomarker [6,35]. For instance, during perinatal adverse events, such as asphyxia, HPA axis is activated and consequently, increased serum cortisol levels are found [36]. Cortisol levels are measured as stress biomarker in plasma, saliva, and urine samples using methods based on enzyme linked immunosorbent assay (ELISA) and high-performance liquid chromatography (HPLC) with great accuracy, limits of quantification of less than 1 μg/nL, and less than 20% of coefficient of variation [6,33–36]. It should be highlighted that HPLC allows the simultaneous determination in the same assay of different compounds apart from cortisol that include catecholamines, providing more information with the same sample size [34].

4.2. Conundrum of alpha amylase in the perinatal period

The most common serological measures of autonomic activation are both plasma catecholamines, epinephrine and norepinephrine. However, the measurement of catecholamines in non-invasively obtained biofluids by HPLC or immunoassay has proven extremely difficult, and does not reflect the activity of the central nervous system. As a consequence, non-invasive surrogate markers have been actively sought. The action of norepinephrine upon the salivary glands rich in β-adrenoreceptors promoting the protein-to-fluid ratio, and among these the α-amylase in the saliva has been increasingly employed to indirectly measure the activity of NE as response to stress stimuli [37–39]. Seemingly, important as it would be to include α-amylase in the screening for stressful situations in the newborn period, however, its applicability is limited because the maturation of the salivary glands is not achieved until later in infancy and therefore changes in its composition in response to norepinephrine are lacking [40]. In a recent study, no differences in the levels of α-amylase were detected in the newborn and at 3 months in response to stress [41].

4.3. Other stress biomarkers

Enzyme immune analysis (EIA) allows to determine a series of additional stress biomarkers such as Copeptin which reflects perinatal stress associated with delivery mode [42], cytokines highly expressed as a consequence of stressful stimuli [43], and plasma oxytocin, associated with lower infant social engagement, or impaired social behaviour [44].

Also, to investigate if oxidative stress is involved in stressful medical procedures, some oxidation protein products and hydroperoxides have been determined in blood samples from full-term newborns during heel prick, observing a relationship between crying behavioural parameters and oxidative stress biomarkers levels [45].

Among other potential stress biomarkers, it was observed that levels of 17-hydroxyprogesterone in newborns' blood are highly sensitive to stressful stimuli [46]. This biomarker has been determined using immunoassay with satisfactory analytical performance [45,46]. However, most of these studies are based on biomarkers determined in blood samples with the consequent stress response associated to sampling that may invalidate the results [47].

5. Non-invasive biomarkers for stress monitoring

To accurately evaluate the level of stress, it seems reasonable to avoid the concurrence of a stressful intervention such as venepuncture or heel prick with analysis of a sample obtained. Therefore, non-invasively obtained samples have become generalized and a promising approach (Table 1). In this sense, saliva sampling is the most employed

Table 1
Non-invasive biomarkers for newborns stress monitoring.

Reference	Sample	Analysis technique	Biomarker	Results
[6]	Saliva	UPLC-MS/MS Kinetic enzyme assay	Cortisol α-amylase	Reference levels for cortisol and alpha-amylase were stablished. It could be applied to further clinical research on determination of perinatal and postnatal stress
[33]	Saliva	luminescence immunoassay	Cortisol	The trajectory of maternal cortisol across gestation was associated with the infant cortisol response to the heel-stick stressor.
[35]	Saliva	Enzyme Immunoassay kit	Cortisol	Newborns that received full rooming-in care (24 h) show lower cortisol levels compared to partial (14 h) rooming-in care.
[48]	Saliva	Enzyme-linked immunosorbent assay (ELISA)	Cortisol	Higher pain-related stress exposure during NICU stay was linearly associated with lower salivary cortisol reactivity to the Face-to-Face Still-Face procedure at 3-month age
[49]	Saliva	Enzyme Immunoassay kit	Cortisol	Salivary cortisol concentration was not significantly altered in infants after applied a noxious test.
[51]	Saliva	Luminescence enzyme assay Kinetic reaction assay	Cortisol α-amylase	α-amylase increases after an exam/inoculation stress protocol at 6 and 12 months, but not at 2 or 24 months of age. Cortisol increases at 2 and 6 months, but not at older ages.
[52]	Saliva	Radioimmunoassay	Cortisol	Elevated in newborns in a NICU compared to newborns that were sent to their own homes
[53]	Saliva	ELISA-Kit	Cortisol	Decrease in mothers after skin-skin contact mother-infant, while in infants there were found variable cortisol levels that do not indicate stress reduction.
[54]	Saliva	Enzyme immunoassay kit	Cortisol	Comparing changes in stress reactivity they found that tactile-only group infants had highest cortisol levels, followed by control group infants and infants who received a multisensory intervention.
[55]	Saliva	Enzyme immunoassay Enzyme immunoassay	Cortisol Oxytocin	Salivary Oxytocin levels increased significantly during SSC for parents and infants. Infant cortisol levels decreased significantly during SSC.
[57]	Saliva	Multiplexed bead immunoassay	Cytokines	There were a positive association between IL-6 and stress. The cytokine levels were different between preterm and fullterm children and appear to be influenced by stress situation and/or antigenic microbial challenge.
[61]	Saliva Urine Umbilical blood cord	Enzyme immunoassay Enzyme immunoassay Radio immunoassay	Cortisol	Usability rates of cortisol as biomarker were 80.6% (cord blood), 85.9% (saliva), and 93.5% (urine).
[34]	Urine	HPLC	Dopamine, epinephrine, norepinephrine	Urinary norepinephrine levels were slightly higher in the group of children born small for gestational age compared to control group after a stress test.
[60]	Urine	Enzyme immunoassay kit	Oxytocin	Plasma oxytocin decreased with age, at a rate of 15% per week, and exhibited strong stability within infants, Urine oxytocin was not correlated with plasma oxytocin and did not show a significant trend over time.
[68]	Umbilical cord plasma	Immunofluorescent assay	Copeptin	Higher levels in intrauterine growth restriction infants than in appropriate gestational age controls
[70]	Umbilical cord plasma	Enzyme immunoassays	Atrial natriuretic peptide, brain-type natriuretic peptide	High levels were associated with prematurity at birth, uteral contraction and antenatal stress.
[62]	Hair	Enzyme immunoassay kit	Cortisol	Hair cortisol shows intraindividual stability that can be used as chronic stress biomarker.
[63]	Hair	LC-MS/MS	Cortisol	Mild perinatal adversity may act as a susceptibility factor, moderating environmental effects. Elevated cortisol stress reactivity has been suggested to be a marker of enhanced susceptibility to the environment.
[65]	Nails	LC-MS-MS	DHEA or DHEA sulfate	DHEA, but not DHEA sulfate, was increased in infants of mothers with stressful life events during pregnancy.

matrix in the evaluation of several physiological mechanisms related to newborns [48]. Specifically, it is useful in the measurement of both basal levels of stress and response to stressful stimuli, since its simple sampling does not lead to increased stress, while blood sampling could do so. For this reason, serial salivary determinations have been a simple and useful solution for monitoring stress response. Among salivary stress biomarkers, cortisol, as a regulator of the autonomic nervous system [35,49] is the most assayed [50]. In general, salivary cortisol is measured by immunoassay and only a few studies have used analytical methods based on ultra-performance liquid chromatography (UPLC) [33,35,48,49,51–56]. The sensitivity achieved to quantify salivary cortisol using immunoassay is satisfactory; however, it shows poor specificity and high cross-reactivity with other compounds such as cortisone or corticosterone [53]. On the other hand, UPLC-based methods show high specificity, but the expensive equipment required constitutes an important drawback for its routine clinical use.

Salivary α-amylase is determined by immunoassay, this method shows high sensitivity, requires a previous dilution step of the samples and shows satisfactory precision (coefficients of variation $< 15\%$) [56]. Salivary oxytocin is also measured by a previous validated immunoassay to evaluate the reduction of stress levels produced by skin-to-skin contact between parents and newborns [55]. Moreover, inflammation mediators, such as cytokines were determined in saliva by multiplex immunoassay, showing that interleukin 6 is influenced by the stress situation [57]. However, saliva sampling has some limitations since some factors can influence salivary composition (caries, periodontal disease), so it is important to identify the biomarkers alteration between systemic and oral disease [58]. In addition, the secretion rate influences the metabolites concentration, so sampling should be carried out without stimulation in order not to alter its composition [59].

Among other non-invasive biological samples, it is important to highlight urine. In this matrix, high norepinephrine levels were found in children born small for gestational age after a stress test [34]. This analyte was determined by HPLC with the advantage that other catecholamines could be studied simultaneously. In addition, urinary oxytocin (OT) was determined by immunoassays with great precision in extremely preterm infants as a neurodevelopment biomarker, and authors considered that further research was required in order to explore the dysregulation of the stress response as a potential mechanism contributing to impaired OT levels [60]. Also, cortisol has been determined in urine samples by means of immunoassays showing a higher utility than saliva or spinal cord samples [61]. Nevertheless, since differences in renal function influences the results of the different metabolites in urine samples, creatinine levels should be determined [60].

Finally, hair is also a promising biological sample to evaluate chronic stress in newborns by means of the cortisol levels, since they showed a suitable intra-individual stability [62,63], and cortisol in these samples has been measured by ELISA and HPLC. In the same way, nails can be used to evaluate the effects of stressful life events during pregnancy by means of determination of dehydroepiandrosterone (DHEA) or DHEA sulphate levels [64]. But this type of sample reflects accumulated stress levels and there is a lack of prospective studies about the relationship between cortisol levels in hair and the onset of mental disorders [65]. In addition, these determinations require additional sample treatment steps to remove sample interferences [62] and this is out of the scope of this review.

To summarize, cortisol is the most used stress biomarker but in the last few years new stress biomarkers such as cytokines, oxytocin or catecholamines have appeared, and also new promising non-invasive samples like hair or nails with the advantage of simple sampling to monitor stress without altering biomarker levels.

Practice points

- Diagnosis of acute and especially of chronic stress in the NICU is based on subjective evaluation of newborn infants' reactivity using clinical scoring systems thus lacking of objective measures.
- The use of sedation and analgesia further difficulties the assessment of stressful situations by the caregivers.
- The use of blood biochemical monitoring causes pain and stress to the baby and therefore alters plasma hormone levels rendering inefficacious.
- Saliva is a non-invasive and easily obtained matrix in which progressively more and more biomarkers of stress can be reliably determined, especially cortisol and oxidative stress metabolites.

Future directions

- The development of cot-side easy to interpret and reliable non-invasive methods to evaluate stress hormones especially catecholamine derivatives in urine and stress hormone derivatives in saliva.
- The big data analysis of continuously monitored physiological parameters such as heart rate, temperature, amplitude integrated EEG or arterial blood pressure.
- The development of algorithms integrating clinical, physiological and biochemical parameters with predictive value of the consequences of acute/chronic stress upon patients' health in later stages of life.

Conflicts of interest

The authors report no conflict of interest.

Appendix. Analytical methods developed for determination of biomarkers in saliva

Our group has substantial experience in determining non-invasive stress biomarkers, such as cortisol and α-amylase in saliva samples [66–70]. Saliva was collected in sterile bottles between 10 and 12 a.m. (minimum 1h after eating) and aliquoted into 1.5 mL tubes and stored at −80 °C until analysis. The sample treatment was based on previous work [6] (see Fig. 2). First, 50 μL of saliva sample were added to H2O (0.01% (v/v) acetic acid), and 5 μL of internal standard solution (600 nmol L-1 sulfadimethoxine). Then, liquid-liquid extraction (LLE) was carried by means of ethyl acetate and sonication. After that, ethyl acetate layers were evaporated to dryness using the speed vacuum concentrator. The residues were reconstituted in 100 μL of H2O:CH3OH (85:15, v/v, and 0.01% acetic acid) and injected in the chromatographic system coupled to tandem mass spectrometry (UPLC-MS/MS). This system consisted of a Waters Acquity UPLC-Xevo TQD system (Milford, MA, USA). Detection was carried out under positive electrospray ionization and chromatographic separation by using an Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm) and a binary mobile phase CH3OH (0.01% v/v CH3COOH):H2O (0.01% v/v CH3COOH) with gradient elution.

In this way, the developed analytical method was validated obtaining satisfactory limits of detection for cortisol ($0.2\,\text{nmol}\,\text{L}^{-1}$), as well as high precision (coefficients of variation 12–16%) and accuracy (recoveries 70–109%). Then, the corresponding reference ranges for cortisol were established for newborns and mothers at different perinatal periods [6], observing that the lower levels were obtained at 38 weeks of gestation for mothers and no differences were observed for newborns between birth and 3 months of age.

In addition, other studies applying the previous analytical method have been carried out to evaluate the effect of maternal age over stress-related variables in women [67], to predict preterm birth in pregnant women with threatened preterm labour [66], and to evaluate the influence of in-vitro fertilization over cortisol levels from pregnancy to postpartum period in women [68].

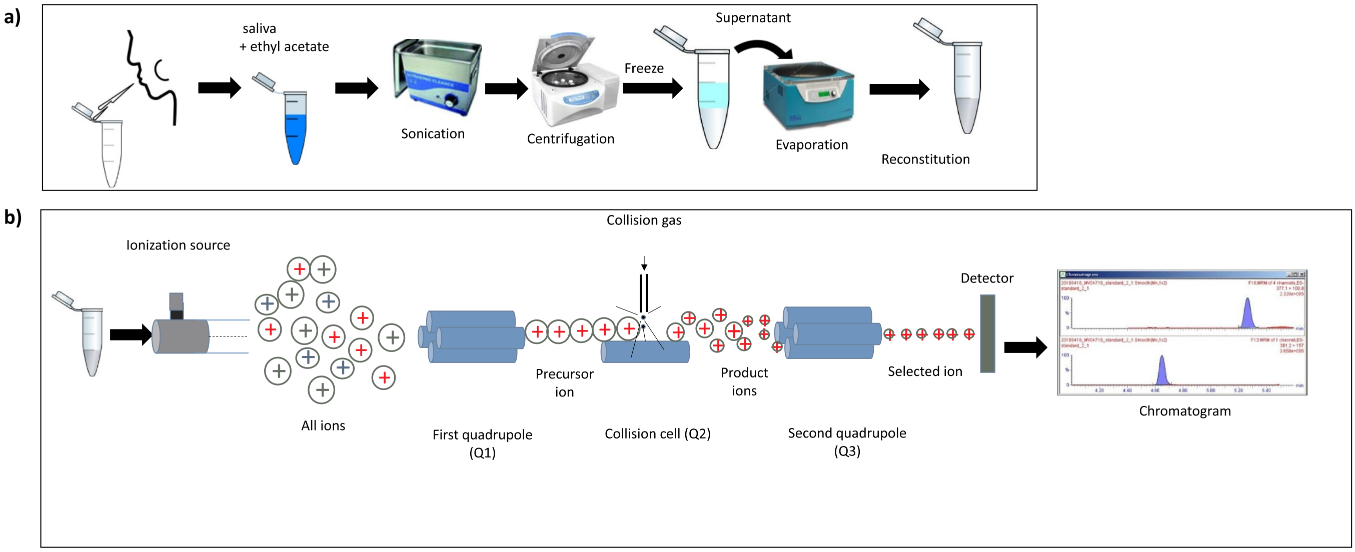

Fig. 2. Diagram representing the methodology to determine salivary stress biomarkers (developed in reference # 8). a) Scheme of saliva sample treatment. b) Scheme of a triple quadrupole mass spectrometer.

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Assessment of pain in newborn infants

Mats Eriksson[a,*], Marsha Campbell-Yeo[a,b,c]

[a] Faculty of Medicine and Health, School of Health Sciences, Örebro University, S-701 85, Örebro, Sweden
[b] School of Nursing, Faculty of Health, Departments of Pediatrics, Psychology & Neuroscience, Dalhousie University, 5850/5890 University Ave, Halifax, NS, B3K 6R8, Canada
[c] Centre for Pediatric Pain Research, IWK Health Centre, Halifax, Canada

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ABSTRACT

Hospitalized newborn infants experience pain that can have negative short- and long-term consequences and thus should be prevented and treated. National and international guidelines state that adequate pain management requires valid pain assessment. Nociceptive signals cause a cascade of physical and behavioral reactions that alone or in combination can be observed and used to assess the presence and intensity of pain.

Units that are caring for newborn infants must adopt sufficient pain assessment tools to cover the gestational ages and pain types that occurs in their setting. Pain assessment should be performed on a regular basis and any detection of pain should be acted on. Future research should focus on developing and validating pain assessment tools for specific situations.

1. Introduction

There is no longer any doubt that newborn infants experience pain, and that this pain can have negative consequences on short and long term outcomes. Ever since the publication of the first national and international guidelines for neonatal pain management [1,2], pain assessment has been promoted as an essential part of adequate pain management. The purpose of pain assessment is to judge if an infant is in pain and if so, take action to reduce or remove that pain. Pain assessment is also needed to evaluate the effect of interventions aimed at pain relief, both on individual and institutional levels.

2. Types and sources of pain

The International Association of Pain (IASP)'s classical definition of pain from 1969, as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [3], has since been discussed in relation to how newborn infants can communicate their experienced pain and how it can be interpreted by caregivers [4]. Traditionally three types of neonatal pain have been mentioned when discussing how to assess pain: acute/procedural pain, acute/prolonged pain (including post-operative pain), and chronic pain. Having only these three definitions of pain-types has limited the development of a more finely-tuned pain assessment, and thus in 2017 Anand proposed an updated uniform taxonomy, based on temporal features, character of pain and secondary effects [5]. Built on these three features he suggested the following terms to classify neonatal pain: Acute episodic, Acute recurrent, Prolonged, Persistent, and Chronic.

All infants, even those considered to be healthy, undergo painful procedures immediately after birth and throughout infancy as part of routine preventive practices. Exposure to pain and repeated painful procedures is even greater in sick and/or preterm newborn infants due to their medical condition but mostly as a result of the care and treatment they receive. Numerous studies show that hospitalized neonates undergo 10–15 painful procedures daily, both in industrialized [6,7] and in developing [8] countries, and often without any associated pain relief [9]. Besides surgery and mechanical ventilation, the most common sources of pain are skin-breaking procedures: heel lance, venipuncture and placement of venous catheters, and non-skin-breaking procedures: endo-tracheal suctioning and insertion and manipulation of CPAP-prongs [10].

3. Consequences of pain

The groundbreaking studies by Anand et al. in the late 1980's demonstrated that the provision of sufficient analgesia reduced negative short-term outcomes in neonates undergoing surgery, which previously had been performed with just muscle-relaxant [11–13]. The stress caused by pain leads to alterations in heart rate, breathing rate, blood

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[*] Corresponding author.
E-mail addresses: mats.h.eriksson@oru.se (M. Eriksson), marsha.campbell-yeo@dal.ca (M. Campbell-Yeo).

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pressure, intracranial pressure, and to hormonal and metabolic changes [14,15]. This in its turn can lead to impaired wound healing, lower immune response and/or cerebral lesions. In addition to the immediate stress and physiological instability associated with pain, more recent studies have shown that greater exposure to repeated painful procedures in early life is associated with long lasting adverse effects such as alteration of later pain response, delayed postnatal growth, poor early neurodevelopment, and altered brain development [16–18].

4. Pain signaling

In adult and cognitive intact persons self-report is the gold standard for detecting the presence, type and intensity of pain, but in non-verbal persons like newborn infants, responses in different bodily systems must be the base for pain assessment. When peripheral pain receptors (nociceptors) are affected by mechanical (or chemical or thermal) stimuli - usually tissue damage from e.g. a heel lance - pain signals are transferred in nociceptive pathways, to the spinal cord. There, a spinal reflex response is induced with the purpose to withdraw the affected limb, away from the threat/hurt. Simultaneously pain-signals are sent to different areas in the brain where further physiological, hormonal and behavioral responses are produced [19]. The purpose of these reactions is to protect the human being from further damage, but immaturity, illness, brain deprivation or sedation affects the ability to react adequately [20]. This means that pain assessment methods that are built on these reactions also must take contextual factors like gestational age and medical status into account. This paper focus on pain assessment in newborn infants, i.e. up to 4–6 weeks after full term birth. Some signals and pain assessment tools are valid also for older ages but most research has been in the preterm population.

The normal response to a painful stimulus is a vivid activation of mechanisms to facilitate the avoidance of hurt and danger. Repeated pain signaling will however change these reactions with an increased sensitivity – hyperalgesia – and even response to non-painful stimuli – allodynia [21,22]. If the pain continues and become prolonged or even persistent the reactions might be blunted [23]; as such absence of - or lower - pain signals cannot be assumed to equate to the absence of pain. Given this possibility, different pain assessment methods that are developed and validated for specific situations should be considered when evaluating acute or prolonged pain [24].

4.1. Biomarkers

Table 1 demonstrates physiological and neurophysiological reactions, also called biomarkers [25,26], that can be used as indicators of pain in infants. Given that many of these signs are dependent on the infant's ability to react, and thus both an increase and decrease can be seen. Normally a healthy robust infant born at term age will react with an activation of the fight-flight system including increased heart and respiration rate, dampness of palmar and plantar skin etc., whereas infants delivered preterm or ill, or those in a sleep-state will exhibit a lower or reverse response [15,27,28]. While the activation of the fightand flight mechanism includes the release of stress hormones, e.g. catecholamines and corticosteroids [25], the requirement of laboratory analyses makes them less appropriate for clinical practice and they will not be further presented in this paper. Pain signals can also be detected with modern neuro-imaging techniques like electroencephalography.

EEG, near-infrared spectroscopy (NIRS), or functional magnet resonance imaging (fMRI) [29]. Despite these methods holding promise for improved pain assessment in non-verbal infants, considerable challenges remain regarding the pain specificity, clinical utility and feasibility of these techniques [30,31]. Detailed discussion of these techniques is beyond the scope of this paper.

4.2. Behavioral pain signaling

Pain leads to a number of responses in the infant's behavior, that can be observed and contribute to assessment of presence and intensity of pain [15]. These responses include changes in body movements and tone, grimacing, crying or vocalization, changes in sleep-wake state and affected attention/communication. Similar to physiological responses, prematurity, illness or lower wake-state can lead to more diffuse behavioral signs when compared to those exhibited by healthy full-term infants. It is suggested that behavioral signs, especially facial expressions, are more pain specific than physiological signs, which can alter in response to many situations: pain, stress, discomfort or touch [46] (see Table 2).

4.3. Pain assessment tools

Infant pain measures are often classified as being either unidimensional or multidimensional. Unidimensional measures include a) single item, e.g. changes in heart rate, b) single domain when more than one item in the same domain is included, e.g. facial expressions, or c) multiple domain with items from different domains within the same dimension, e.g. movements and facial expressions which are both in the behavioral dimension. In contrast, multidimensional measures, often referred to as composite, include items from more than one dimension, often behavioral, physiological reactions and infant factors e.g. state. Some studies suggest that behavioral items have greater effect size, i.e. influences the overall pain assessment more that their physiological companions when combined in the same instrument [54,55].

There have been several attempts to develop reliable, valid and clinically feasible instruments for newborn infants. To date, around 40 instruments have been published [56], with varying degrees of psychometric evaluation [57]. In Tables 3–5 we list instruments most commonly reported as part of research studies, considered to be reliable and valid in this population, and those with the greatest uptake across clinical settings worldwide. We have excluded instruments that have been locally developed and adapted, or those considered to be “out-

Table 1
Physiological and neurophysiological reactions to pain. For a comprehensive overview, see Refs. [25,26], whereas more specific references if necessary are given in the table.

	Effect from painful stimuli	
Blood pressure	Increase or decrease	
Heart rate	Increase or decrease, bradycardia	
Cerebral oxygenation	Increase of oxy-haemoglobin (HbO2) and decrease of deoxy-haemoglobin (HHb))	[32,33]
Electroencephalography (EEG)	Evoked response over central brain regions	[34,35]
Flexion withdrawal reflex	Threshold increases in latency and amplitude	[36,37]
Heart rate variability	Decreased spectral power in the high frequency band	[38–40]
Intracranial pressure	Increase	[41]
Oxygen saturation	Decrease	
Respiration rate	Increase or decrease, apnea	
Skin color	Increase (red) or decrease (pale)	[42]
Skin conductance	Increased number of peaks/second, amplitude of peaks and area under curve	[43–45]

Table 2
Behavioral reactions to pain. For a comprehensive overview, see e.g. Ref. [15], whereas more specific references if necessary are given in the table.

	Effect from painful stimuli	
Communication	Avoidance of eye-contact, locking of gaze or drifting away	
Crying, vocalization	Longer duration, changes in quality; fussiness, "silent cry"	[47,48]
Facial expressions, grimacing	Presence and duration of e.g. brow bulge, eye squeeze, naso-labial furrow, open lips, horizontal mouth stretch, vertical mouth stretch, lip purse, taut tongue and/or chin quiver	[49,50]
Limb movements	Presence and duration of avoiding or more indistinct limb movements; hand movements like fisting or finger splaying	[15,51–53]
Muscle tone	Increased or decreased	
Sleep-wake state	Quality of sleep, hyper-alertness	

dated" and replaced with successors, or where no further validation studies are published. Some authors have also suggested that the body movements associated with NIDCAP®-observations can be used to assess pain [51,58], whereas other did not find them pain-specific enough and thus should not replace e.g. facial expressions as pain-measure [59].

4.4. *Subjective pain rating*

Besides giving scores to observable or measurable pain signs, some pain instruments, like COMFORTneo and PAT, includes 1–2 items where the person who is performing the assessment should give his or her own rating of pain and distress [68,77]. Bellieni et al. argued that pain *detection* is more important than pain scoring in the everyday clinical situation, and thus suggested a two-point method for this. First step is to judge if the situation could be painful and secondly to look for a reaction, e.g. crying or changes in heart-rate [82]. This can however be hard. In a study from a British NICU without routine use of validated pain tools, 50% of the staff found it difficult to determine whether a baby was in pain or not [83].

5. Pain assessment by parents

In a family centered neonatal care approach, it is natural to engage parents in pain management and pain assessment, and they have also expressed this wish [84,85]. To ensure infants optimal pain management built on parental assessment, it is important to know if the parents are able to perform an adequate pain assessment. In two studies from Brazil, mothers without previous training were able to identify signs of procedural pain [86], primarily related to crying and restlessness. Interestingly, these mothers did not consider facial expressions as being associated with pain signaling [87]. In a study comparing parents' and health care professionals' ability to recognize photographs of a "pain face" (i.e. no relation between the newborn infant and the observer), the parents were slightly more able to recognize the pictures of a painful situation [88], whereas parents in clinical studies tend to rate pain lower than health care professionals [89], or perceive a higher degree of distress than of pain in their infants [90]. Boyle et al. found that parents thought it was easy to assess their infant's *comfort.* The word pain was not used when asking the parents, which indicates the importance of a common terminology. The parents also believed that it was easy for the staff to assess their infant's pain, which was not confirmed by the staff in the same study [83].

In studies on older children the parents underestimated their child's acute or postoperative pain, which per se leads to a risk of undertreatment [91–93]. Built on an interview-study with parents, Loopstra et al. have suggested a model for parental assessment of acute child pain, built on how parents can regulate their own feelings and be open for the baby's pain cues [94].

6. Assessing pain experiences or pain responses?

While it was previously believed that infants' reactions to pain were simply reflexive, we now know that all the systems needed for ascending pain processing are present early in the fetal development (whereas the descending pain modulatory functions mature later). We still have little knowledge whether a newborn infant is able to *experience* pain in a more affective way, but recent studies using functional brain imaging indicate that the brain regions that encode sensory and affective components of pain are active in infants, suggesting that the infant pain experience closely resembles that seen in adults [95]. For the time being, methods built on pain *perception* does not seem to have a clinical utility or advantage over those measuring pain *responses* [96].

7. Requirements on pain assessment

No matter which tool we choose for pain assessment it must be valid (measure what it is intended to measure), and reliable (give the same results if repeated by another person or at another time under the same conditions) for the specific population being assessed and feasible to use in the clinical situation [97]. This includes how much time and resources it takes to acquire, implement, train the staff and maintain the use. Meesters et al. argue that pain assessment tools should be able to measure responsiveness, i.e. being able to detect a decreased pain level following prevision of a pain relieving intervention [57]. Given the lack of a single gold standard tool, most National and International guidelines generally include a list of valid and reliable tools rather than recommend a specific pain assessment tool [1,98,99] and emphasize the importance of the implementation and training process. In a systematic review Dovland Andersen et al. reviewed 12 reviews which in their turn reviewed in all 65 pain scales for non-verbal children, and of which 28 were recommended at least once. The authors concluded that the evidence quality of the reviews was low, and thus their recommendations for what scales to use should be interpreted with caution [100].

As seen in Tables 3–5, there seems to be a sufficient number of instruments for acute and prolonged pain in preterm and term infants. Little is however known about how accurate they are for assessing pain in extremely preterm (before 28 weeks' gestation) or for infants in specific conditions, e.g. undergoing hypothermia. It can also be argued the advantage of instruments that take contextual factors like gestational age into account, e.g. the Premature Infant Pain Profile [79,80].

Table 3
Unidimensional single domain pain instruments. References indicate development and validation publications.

Instrument	Included items	Validated for pain type and age	
ABC scale	Acuteness, rhythmicity and continuity of crying	Acute procedural pain in preterm and term infants	[60,61]
NFCS Neonatal Facial Coding System	Brow bulge, eye squeeze, naso-labial furrow, open lips, horizontal mouth stretch, vertical mouth stretch, lip purse, taut tongue, chin quiver	Acute procedural pain, post-operative pain. A simplified bedside version was published 1998 [62].	[50]

Table 4
Unidimensional multiple domain pain instruments.

Instrument	Included items	Validated for pain type and age	
BIIP Behavioral Indicators of Infant Pain	Behavioral state, brow bulge, eye squeeze, naso-labial furrow, horizontal mouth stretch, taut tongue, finger splay, fisting	Acute procedural pain in preterm and term infants	[53,63]
BPSN Bernese Pain Scale for Neonates	Alertness, duration of crying, time to calm, skin colour, eyebrow bulge with eye squeeze, posture, breathing pattern	Acute procedural pain in preterm and term infants	[64,65]
CHIPPS Children's and Infants' Postoperative Pain Scale	Crying, facial expression, posture of the trunk, posture of the legs, motor restlessness	Post-operative pain in term infants (and children up to 4 years)	[66,67]
COMFORTneo Scale	Alertness, calmness/agitation, respiratory response, crying, body movement, facial tension, body muscle tone. NRS[a] estimate of pain and NRS estimate of distress	Prolonged pain in preterm and term infants. Also validated for sedated infants.	[68]
DAN Douleur Aiguë du Nouveau-né (English name: Acute Pain in Newborns - APN)	Facial expression, limb movement, vocal expression	Acute procedural pain in preterm and term infants	[69]

[a] NRS = Numeric Rating Scale.

8. The use of pain assessment

Many authors have studied the implementation and use of structured pain assessment in clinical practice, and the results are discouraging. A prospective cohort study in 243 neonatal intensive care units from 18 European countries found that only 32% of the 6648 infants received at least one assessment of continuous pain and that only 10% had daily pain assessment [101]. Some countries have come further, e.g. a Dutch study showed that most of the NICU-patients had at least one pain assessment during their hospital stay [7]. The percentage of units which report that they have implemented and are using a structured pain scale varies between countries from 6 to 88% [102–107], and in a survey of neonatal nurses in the USA, 81% reported that their unit used a pain assessment tool regularly [108].

9. How to implement and maintain pain assessment

Despite existence of published clinical guidelines for two decades [1,2] reporting that optimal pain management starts with adequate pain assessment, compliance remains low. Franck and Bruce reviewed the literature and concluded that there is a lack of good-quality evidence for efficacy, effectiveness or cost-benefit of standardized pain assessment tools in relation to pediatric patient or process outcomes [109]. Stevens et al. investigated different knowledge transition (KT) strategies to bridge the gap from pediatric pain research to practice but found that no specific type of single or combination of KT strategies was more effective in improving pain assessment and management outcomes [110].

It has often been said that pain assessment should be the “fifth vital sign” [111] but as such, health care professionals must also know how to interpret the assessment and what action to take. For example, every performed pain assessment should lead to a discussion and decision regarding next steps in clinical decisions to reduce pain, otherwise the assessment merely represents a number on a chart rather than guiding care. The use of a flowchart or algorithm is a helpful tool to ensure that all infants receive adequate pain management, irrespectively who performed the assessment or who has the medical responsibility on that shift [112]. It is also advisable to perform audits or benchmarking on regular basis, to ensure that the unit maintains compliance with the guidelines [113].

10. Novel and future pain assessment

This review focuses on pain assessment methods that are clinically useful in today's neonatal care settings. There are however some interesting novel techniques, or novel applications of known techniques that might be clinically useful in the near future, or that will provide new insights that helps us understand pain assessment better. Many of the methods that focus on brain activity associated with nociception have initially been developed in adult brain research [114] and subsequently been adapted to newborns. In some studies electroencephalography (EEG) has shown noxious-specific activity in term infants [34,115,116], whereas others found no pain-related biobehavioral responses [117]. Near Infrared Spectroscopy (NIRS) measures cerebral hemodynamics by recording oxygenated (HbO2) and deoxygenated (HHb) hemoglobin; an increase in HbO2 and decrease in HHb

Table 5
Multi-dimensional pain instruments.

Instrument	Included items	Validated for pain type and age	
ALPS-Neo Astrid Lindgren and Lund Children's Hospital's Pain and Stress Assessment Scale for Preterm and Sick Newborn Infants	Facial expression, breathing pattern, tone of extremities, hand/foot activity, level of activity	Prolonged pain in preterm and term infants	[70]
CRIES (Acronym of the included items)	Crying, requires oxygen, increased vital signs, expression, sleepless	Prolonged pain in preterm and term infants (and children up to 6 years)	[71,72]
EDIN Échelle Douleur Inconfort Nouveau-né	Facial activity, body movements, quality of sleep, quality of contact with nurses, consolability	Prolonged pain in preterm infants	[73]
NIPS Neonatal Infant Pain Scale	Facial expression, cry, breathing patterns, arms, legs, state of arousal	Acute procedural pain in preterm and term infants	[74,75]
N-PASS Neonatal Pain, Agitation and Sedation Scale	Crying/irritability, behavior state, facial expression, extremities tone, vital signs	Acute procedural pain, prolonged pain (post-operative and during mechanical ventilation) in preterm and term infants	[76]
PAT Pain Assessment Tool	Posture/tone, sleep pattern, expression, colour, cry, respirations, heart rate, oxygen saturation, blood pressure, nurse's perception	Post-operative pain in preterm and term infants	[77,78]
PIPP, PIPP-R Premature Infant Pain Profile (-Revised)	Gestational age, behavioural state, heart rate, oxygen saturation, brow bulge, eye squeeze, naso-labial furrow	Acute procedural pain in preterm and term infants	[79–81]

has been reported to be associated with nociceptive response [33]. NIRS mostly correlates with Premature Infant Pain Profile [118], while it sometimes seems more sensitive than the pain scale [118,119]. Hartley and Slater argue for a composite measure of neonatal pain, combining EEG, NIRS and behavioral/physiological tools [120]. A recent review by Benoit and colleagues examining the methods used to date to assess neurophysiological pain response in infants found that while more methodologically rigorous studies are needed, ERPs derived from EEG appear to hold the greatest promise as indicators of infant nociception during clinical procedures as a means to supplement existing measures [30].

There are other previously studied behavioral, physical, and neurophysiological reactions where modern equipment and advanced computer software may provide a new role in clinical pain assessment. Examples are skin conductance [45,121], heart-rate variability [38,39] and cry analysis [47]. Another promising technique is artificial intelligence/machine learning to analyze large amounts of data from clinical surveillance, laboratory tests and facial expression [122,123].

11. Conclusion

Although we know the importance of pain assessment to ensure optimal pain treatment for newborn infants, health care providers must increase the uptake of valid and reliable pain assessment tools, and also ensure that they are used properly. Researchers need to continue validating existing tools for specific situations or patients like extremely preterm infants or infants treated with hypothermia.

11.1. Practice points

- Pain assessment should be performed on a regular basis with a frequency decided by medical condition and by the previous assessment.
- The result of the pain assessment should be recorded and reported, following an algorithm with specified actions for each level of pain.
- Any unit caring for newborn infants should adopt sufficient pain assessment tools to cover the types of patient they are treating, with the types of pain they are experiencing.

11.2. Research directions

- To develop (when necessary) and validate pain assessment tools for different age groups and medical conditions.
- To gain a deeper understanding on how to measure not only the intensity of pain but also its nature, e.g. duration, type of sensation, localization etc.
- To study the impact of implementing and using a structured pain assessment regime on the medical and developmental outcome.
- Continued examination of optimal implementation and practice uptake related to consistent use of assessment tools and clinical algorithms to guide clinical practice.

Conflicts of interest

Both authors declare that they do not have any conflict of interest.

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Developmental neurobiology as a guide for pharmacological management of pain in neonates

Nynke J. van den Hoogen[a,b,*], Anne R. de Kort[a,b], Karel M. Allegaert[c,d], Elbert A. Joosten[a,b], Sinno H.P. Simons[c], Dick Tibboel[e], Gerbrich E. van den Bosch[e]

[a] *Department of Anesthesiology and Pain Management, Maastricht University Medical Centre+, Maastricht, the Netherlands*
[b] *Department of Translational Neuroscience, School of Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands*
[c] *Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands*
[d] *Department of Development and Regeneration, KU, Leuven, Leuven, Belgium*
[e] *Intensive Care and Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands*

ABSTRACT

Pain in newborn children should be prevented due to negative short- and long-term consequences. A good understanding of the development of the nociceptive system in newborns is necessary to enable optimal pain assessment, and most importantly to treat and prevent pain adequately in neonates. So far, preclinical juvenile animal studies have led to a tremendous amount of information regarding the development of the nociceptive system. In addition, they have made clear that the developmental stage of the nociceptive system may influence the mechanism of action of different classes of analgesics. Age specific analgesic therapy, based on post-menstrual age, should therefore be considered by incorporating information on the developmental stages of the nociceptive system in combination with knowledge from pharmacokinetic and –dynamic studies in neonates.

1. Introduction

The International Association for the Study of Pain (IASP) has defined ’pain’ as ‘*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’* with the note that *‘Pain is always subjective and each individual learns the application of the word pain through experiences related to injury in early life’* [1]. Since pain is subjective, self-report is the golden standard. However, newborns and young children are generally considered unable to express their pain verbally and cannot quantify their pain by self-report. Therefore, other techniques, like parent reports or validated behavioural pain scales used by trained nurses, are needed to optimally assess pain in newborns [2,3].

A good understanding of the development of the nociceptive system in newborns is necessary to improve pain assessment and most importantly in order to treat pain adequately in neonates and eventually prevent pain using the concept of pre-emptive analgesia. We have to bear in mind that major differences exist between tissue damage due to surgical procedures such as intestinal surgery in children with necrotizing enterocolitis and procedural pain such as heel lances. This will have consequences for the choice of analgesic therapy since intravenous paracetamol and morphine are recommended after major surgery while paracetamol and morphine are not recommended for procedural pain [4,5]. Moreover, treating pain is important in preventing the short-term and potential long-term consequences of early life pain on development of the nociceptive system. The use of pre-emptive analgesia during the neonatal phase is thought to play an important role in the prevention of long-term side effects of pain. This is based on animal studies which have shown more negative effects of neonatal pain when pain experiments were conducted in the absence of adequate analgesic therapy [6]. However, exposure to analgesics can also affect development, and especially when administered in the absence of pain. Preclinical studies showed that negative long-term effects of postnatal opioid exposure may differ depending on whether they were given in the absence or presence of pain, with protective effects in the latter case [7–9]. Those animal studies showed degeneration of neurons, apoptosis in brain regions, impaired cued fear extinction, and impaired cognitive functioning after neonatal opioid exposure when administered in the absence of pain [7,10,11], while protective effects of opioid exposure in the presence of pain were observed such as less neurodegeneration [7–9]. With regards to pain behaviour, morphine pre-treated animals displayed significantly less hyperalgesia and recovered faster from a subsequent inflammatory insult compared to controls that did not receive pre-emptive opioids prior to inflammatory pain [8]. Consequently both pain and opioids have neurotoxic effects as found in preclinical studies and especially when animals were exposed to pain in the absence of analgesics or the other way around.

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[*] Corresponding author. Maastricht University Medical Centre+, Department of Anesthesiology and Pain Management, P.O. box 5800, 6202 AZ, Maastricht, the Netherlands.

E-mail address: n.vandenhoogen@maastrichtuniversity.nl (N.J. van den Hoogen).

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Table 1
Overview of developmental stage of the area and mechanism of action of different analgesic compounds provided at neonatal age.

Analgesic	Area of action	Mechanism of action	Stage of development in newborn
Opioids ((remi)fentanyl, morphine, methadone*)	Periphery Spinal cord - Primary afferents (presynaptic opioid receptor) - Pain transmission neurons (postsynaptic opioid receptor) Brain stem - PAG - RVM	Inhibition of neurotransmitter release in the spinal pain gate; inhibition of nociceptive transmission by activation of opioid descending pathway [48]	Facilitatory instead of inhibitory [49]
Paracetamol	Periphery Spinal cord - Pain transmission neurons - Interneurons Brain stem - RVM	Prevention of peripheral sensitization by inhibition of cyclo-oxygenases (COX enzymes) Central action likely includes serotonergic descending pathway amongst others [50]	Serotonergic system is facilitatory instead of inhibitory [46]
NMDA antagonists (Methadone*, ketamine)	Spinal cord & supraspinal areas - Pain transmission neurons in spinal dorsal horn	Prevention of central sensitization [52]	Not assessed in somatosensory system

Abbreviations: NMDA, N-methyl-D-aspartate; RVM, Rostroventral Medulla; PAG, Periaqueductal Grey. The analgesic Methadone* functions via both an opioid and NMDA related mechanism.

The human nervous system is characterized by its plasticity in particular after birth in the newborn and throughout adolescence [12]. Structural and functional fine-tuning of the nociceptive system and spinal circuit is activity-dependent and can therefore be affected by noxious stimuli as well as exposure to analgesics occurring in neonatal life [13,14]. The underlying mechanisms of the potential effects of neonatal pain originate from the on-going brain development after birth, which is highly dependent on the balance between abundant new formation of connecting neurons and degradation of superfluous unused cells. Therefore, neuroapoptosis is a natural feature under these circumstances. Neuroapoptosis can however be increased by toxic effects of some analgesics and sedatives, such as ketamine [15,16].

Since rats are born at a relatively early stage of brain maturation [17], the nervous system of a neonatal rat pup roughly corresponds to that of a prematurely born neonate. Therefore, we have gained a large amount of information regarding the development of the nociceptive system based on preclinical animal models [18–21] (Table 1). It is important to note that translation of these results into the human situation should be done cautiously, as we cannot overlay the time-course of pre- and postnatal development between species.

We know from studies from the past that analgesics are essential in neonatal health care, improving short-term morbidity and mortality [22]. As described before, adequate pre-emptive analgesic therapy might even play an important role with regards to the long-term effects of pain [6].

Obviously, it is unethical to study the effects of pain in the absence of analgesics using placebo-controlled designs in the human newborn. Histological studies on the effects of pain and analgesics can only be conducted in animals. Besides information regarding the development of the nociceptive system in newborns, preclinical studies are very valuable in studying the long-term effects of neonatal pain. Early exposure to pain and stressful interventions have been associated with neurotoxicity in animals [6]. For example, pain induced by an invasive inflammatory reaction caused alterations in the spinal neuronal circuits at least in rodents [23], and severe inflammatory and procedural pain stimuli caused increased apoptosis in the brains of neonatal rats [7]. With regards to pain sensitivity, exposure to inflammatory pain in early life resulted in decreased baseline nociceptive sensitivity at adult age, and enhanced hyperalgesia after a subsequent inflammatory insult [24,25]. Repeated skin-breaking procedures in animals induced acute hypersensitivity but did not affect basal nociceptive thresholds later in life [14]. Despite this increase of knowledge into the effects of neonatal pain based on preclinical studies, the options for clinical measurement of pain in newborns are still limited. If we fully understand the nociceptive system of newborn children, we can treat pain with targeted analgesic therapy. This targeted treatment should also be based on our increased knowledge about developmental pharmacology and non-maturational factors that might influence the pharmacokinetics and -dynamics of analgesic therapy in newborns such as pharmacogenetics [26–28].

2. Development of the nociceptive system

Newborns are exposed to repetitive nociceptive input and are treated with analgesics during a vulnerable time frame for the central nervous system [29]. The use and effects of analgesics during this timeframe when the nociceptive system is rapidly developing is not yet fully understood. To clearly understand the optimal targets for analgesia in this developing system, knowledge of the functional development of the nociceptive system after birth is necessary.

The functionality of signalling pathways involved in pain perception of newborn infants differs from adulthood, as directly after birth, the somatosensory network still requires maturation at several levels [19,21]. In adulthood, specialized peripheral endings (nociceptors) contain nociception specific receptors responding to mechanical (Piezo1, Piezo2, TRPA1), chemical (ASICs), and thermal (TRPV1, TRPV2) stimuli. The activation of the peripheral endings of the nociceptive fibres results into enhanced generation of action potentials and transmission via primary afferents to the dorsal root ganglion (DRG) and further to the dorsal horn, an important hub of pain processing. Proprioceptive and tactile stimuli are transmitted by thickly myelinated Aα and Aβ fibres respectively, while thinly myelinated Aδ or unmyelinated C fibres transmit nociception specific signals. In the dorsal horn, the primary afferents synapse onto nociception specific (NS) or wide dynamic range (WDR) transmission neurons. In addition, excitatory and inhibitory interneurons are present throughout the dorsal horn, modulating pain transmission in a certain spinal segment. The inhibitory interneurons, containing neurotransmitters glycine and Gamma-Aminobutyric acid (GABA), are an important player in the 'pain gate', and can ensure a decrease in pain transmission once activated [30].

The nociceptive signal is transmitted from spinal cord to supraspinal areas via the spinothalamic tract. From the thalamus, nociceptive signals are transmitted to the somatosensory, cingulate, and insular cortex and the amygdala amongst other structures, where the localization, intensity and perception of pain occurs. Signals arriving in brainstem areas like the Rostral Ventromedial Medulla (RVM) and Periaquaductal Grey (PAG) lead to activation of descending pathways, which in turn modulate the nociceptive transmission in the spinal cord. In adulthood, painful stimuli that are prolonged and inescapable are particularly effective for activating our endogenous opioid system within the PAG and the RVM, important components of the descending inhibitory control of pain in the spinal cord [31]. Deep somatic, visceral or repetitive superficial pain activates the ventrolateral PAG (vlPAG) and elicit long duration, opioid-dependent analgesia [32–34].

3. Nociception during the neonatal period

Immediately after birth, the somatosensory system undergoes postnatal maturation at peripheral and central levels. It is important to note that the nervous system of infants born prematurely is even more immature at birth and will undergo more postnatal reorganization. Primary afferents will undergo activity dependent reorganization [13]. Peripherally, sprouting and pruning of Aβ and C fibres occurs in the late prenatal and early postnatal period [13,21,35]. Additional myelination of Aβ fibres enables faster transduction of somatosensory signals during the first weeks of life [21]. In addition, the central connection of primary afferents undergoes postnatal reorganization. C fibres are the last to enter the superficial dorsal horn, sprouting into Rexed laminae I-II in late prenatal and early postnatal period [36]. After birth, Aβ axons extend into laminae I and II, and withdraw to deeper laminae (III-V) in the first postnatal weeks [13], leading to activation of the superficial dorsal horn by innocuous stimulation. Reorganization of primary afferents in the superficial dorsal horn ensures discrimination between touch and nociceptive signalling in later life. In addition, reorganization of the interneuron population in the dorsal horn develops over the first postnatal weeks, moving towards more targeted modulation of nociceptive processing. More specifically, the GABA and glycine containing inhibitory interneurons mature greatly after birth. In early life, inhibition of fast-acting glycinergic interneurons is less targeted and weaker, developing late in the postnatal period [37]. Interestingly, GABA binding on secondary neurons in the dorsal horn can lead to depolarization instead of hyperpolarization in early life, due to a high chloride (Cl-) concentration and low expression of Cl- co-transporters including potassium chloride cotransporter 2 (KCC2) [38].

Going up to supraspinal processing of nociceptive information, data from human studies become available. It is now clear that around 35 weeks of gestation, neuronal activity of the somatosensory cortex shows discrimination between nociception and touch as assessed by electroencephalogram (EEG) and Near-Infrared spectroscopy (NIRS) [20,39,40]. However, there is no doubt that infants born before 35 weeks of gestation can experience pain [22]. In addition, ample evidence suggests that most areas involved in pain processing are developed around birth, and the newborn brain should be able to process noxious information [20]. However, it is still unclear when exactly the newborn brain is capable of integrating nociceptive information into a painful experience. For an extensive review of the development of the nociceptive spinal cord and brain, the reader is referred to recent reviews on this topic [19,20].

Last to develop in the pain network are the descending tracts, which arise around 36–40 weeks of gestation. While anatomic connections of the descending dorsolateral funiculus are already present at birth as shown by animal studies, descending inhibition is functionally immature throughout the first postnatal weeks [41]. Previous studies have shown that the endogenous opioid system undergoes postnatal developmental changes, at both spinal and brainstem level [42,43]. In the spinal cord, opioid-mediated signalling is stronger in younger animals compared to adults [42]. In the adult PAG, a tonic opioid tone modulates the dorsal horn via the μ-opioid receptor (OPRM1), which is absent in younger animal [42,43].

Serotonergic projections from the RVM to the spinal cord are a major source of descending control in adulthood, facilitating or inhibiting nociception depending on the pain state or the 5-HT receptor subtype that is activated [44]. Serotonergic fibres grow diffusely into the dorsal horn in the term newborn. In the postnatal period, the exuberant sprouting will be pruned and will resemble the adult distribution from P21 on in rodents [45]. A recent paper assessed the development of the descending serotonergic modulation [46]. In early life, the serotonergic descending system facilitates both nociceptive and tactile processing, whereas over the first postnatal weeks this system matures and a switch from facilitation to predominant inhibition of nociception takes place [46]. This is most likely related to functional development of the spinal 5HT receptors [46]. Overall, it is clear that the spinal-bulbo-spinal loop from the RVM is active in early life, but descending modulation arises from spontaneous activity first. Later in development, modulation is mediated by ascending input, and adult patterns start to appear [47].

Box 1 – how do we study postnatal development of the somatosensory system in animals?

To study postnatal development of the somatosensory system, several methods are utilized. A large body of evidence has emerged from rodent studies, which are used as a model for premature (human) births as described before. The development of the nociceptive system in newly born rat or mouse pups resembles the human nociceptive development in its third trimester, and can therefore be used to model prematurely born infants from 24 to 37 weeks of gestation. In rodent models, knock-out or lesion models are used to study the role of a single receptor or a single system in development. In addition, in vivo electrophysiology or electromyography (EMG) are used to assess neuronal activity, and can be related to human EEG or NIRS experiments. To assess neuronal activation after pain in rodents, several pain models are utilized. Acute pain can be studied by injection of irritable, inflammatory chemicals like carrageenan, formalin, or complete Freud's adjuvant [18]. Infliction of tissue damage, either by skin incision in the hind-paw, removal of skin, or needle prick, is used to model different procedural pain modalities. Mechanical sensitivity in newborn rodents can be assessed by dorsal application of Von Frey filaments. In addition, (ultrasonic) vocalisation can be used to assess ‘comfort’ of newborn rodents. For an extensive review of preclinical pain models, the reader is referred to Schwaller et al. [18].

Box 2 – how do we study pain in newborns and children?

Pain assessment in the Neonatal Intensive Care Unit (NICU)

Since pain is always subjective, self-report would be the golden standard. However, as mentioned before, this is impossible in newborns. Therefore observational and behavioural pain scales have been implemented as the current best practice to assess pain in newborns and young children [2,3]. During the last 25 years many different pain assessment tools have been developed showing significant overlap and redundancy of the individual items present in the different pain assessment instruments. To determine acute and procedural pain in preterm and term born children the Premature Infant Pain Profile (PIPP) can be used. The PIPP is validated for both preterm and term born children to measure pain with good construct validity and excellent inter- and intrarater reliability [53]. The PIPP score is based on both physiological and behavioural parameters in newborns. Another very sensitive tool to measure acute pain in newborns is the Neonatal Facial Coding System (NFCS) measuring facial expressions, but only suitable for retrospective analyses of videotapes in research settings [54]. A well-known and often-used scale is the COMFORT(NEO) behaviour scale. This scale is reliable to assess prolonged acute pain and discomfort in newborns [55]. It measures the level of alertness, calmness, respiratory response, crying, physical movement, muscle tone and facial tension of a child. A different commonly used behavioural scale is the Face, Legs, Activity, Cry, Consolability (FLACC) scale. The FLACC is used to quantify pain behaviour and has a high interrater reliability [56]. However, there are insufficient data to support the FLACC scale for use in all circumstances and all populations to which it is currently applied [2]. Despite the high number of available behavioural pain assessment tools they all have their limitations, often only presenting a snapshot of the patient's condition and are not validated to assess the response to analgesic therapy or fail to identify sensitivity to change [57].

Other techniques that hold the promise to improve the measurement of pain in newborns are near-infrared spectroscopy (NIRS), skin conductance and amplitude integrated electroencephalography (aEEG) or cerebral function monitoring (CFM). NIRS measures changes in cerebral haemodynamics in newborns and could detect the effects of painful stimuli on cortical areas of children [58,59]. Newer techniques, such as the Newborn Infant Parasympathetic Evaluation Index (NIPE™), that is based on heart rate variability, still need further evaluation [60].

The lack of a golden standard to measure pain complicates the development of better ways to assess pain in newborns. A previous study compared the Neonatal Facial Coding System with the NIRS and skin conductance in neonates during a painful stimulus [61]. This study showed that during a painful stimulus, NFCS was mildly or moderately correlated with skin conductance and cortical NIRS changes. Previous studies demonstrated that aEEG registration could show evoked responses during pain [40]. While NIRS and aEEG are non-invasive techniques for monitoring pain responses in neonates, these techniques require trained staff to conduct and interpret the recordings. Behavioural and physiological measures are advantageous to aEEG and NIRS for clinical assessment of pain in neonates [62]. Therefore, behavioural pain scales currently still are the most commonly used tools to assess pain at the neonatal care unit. However, premature infants with relatively immature nervous systems display non-discriminative facial behaviours to equally salient noxious and non-noxious inputs, presenting challenges for the interpretation of pain and analgesia in this unique patient group [63]. Future studies on the assessment of pain at the NICU in premature newborns are needed.

Due to the fear for side effects of pharmacological agents, including analgesics and sedatives, their use in the NICU is rather limited. Preterm neonatal care has focussed on non-pharmacological techniques to improve the comfort and development of the preterm infants. For instance, the use of oral sucrose to reduce pain responses to procedural neonatal pain has been thoroughly studied and is currently widely implemented. Its effectiveness in decreasing pain stimuli has been discussed and it is unclear if sucrose could help to reduce the long-term negative consequences of repetitive pain exposure in preterm infants [64].

Experimental pain tests beyond the neonatal period

Besides techniques to measure procedural, acute and chronic pain in newborn patients at the NICU, several tools are developed to measure pain thresholds and pain processing for research purposes. For experimental purposes in children and adults, quantitative sensory testing (QST) is often used to measure detection- and pain thresholds. For instance QST can be used in order to study the potential long-term effects of neonatal pain and opioid exposure [65–68]. QST encompasses a group of assessments with the goal to systematically and quantitatively test the functioning of the nociceptive system. Depending on the type of stimuli, both large myelinated and small myelinated nerve fibres in combination with unmyelinated nerve fibres can be tested, because thermal, pressure, vibration and electrical stimulation can be involved [69]. A commonly used test to determine pain intensity and tolerance is the cold pressor task [70–72]. During this task children immerse a hand or forearm in cold water and give pain scores for the duration of the test. These scores reflect the pain intensity experienced. Furthermore, the immersion time gives information about the tolerance of pain [71,72]. However, it is a qualitative test instead of a quantitative sensory test. The Neurometer (Neurotron, Inc., Baltimore, MD, USA) allows for electrodiagnostic sensory nerve testing [73] but is very painful and therefore unethical to use in children. Moreover, the flexion withdrawal reflex can be assessed using von Frey filaments to test the withdrawal reflex with different thresholds (in milli-Newton). This test can even be used in young children. In premature infants, the flexion withdrawal reflex showed a continuous threshold increase with increasing postnatal age, reflecting changes in spinal cord excitability [74]. In order to test all the different nerve fibres related to detection and pain (Aα, Aβ, Aγ, Aδ, B en C), it would be best to use thermal, electric and chemical stimuli to determine pain sensitivity. However, most of the above-described tests are not possible to conduct in young children because of ethical reasons.

Neuroimaging techniques can used as well to measure brain activity during pain in children such as functional MRI (fMRI). FMRI was first described in 1990 by Ogawa and colleagues [75,76] and detects brain activation based on the blood oxygen level dependent mechanism. It is used frequently for research purposes. Functional MRI can be used to measure brain activation in patients suffering from chronic pain but also in order to measure brain activation during painful stimuli [65,67,77,78]. However, fMRI is currently only usable for research purposes and not yet for clinical purposes to assess pain in children.

4. Pain treatment during the neonatal period

The World Health Organization (WHO) developed a three-step ladder for analgesic therapy [79]. Interestingly, this ladder was designed to treat cancer pain in adults but is very often used in children. The first step of the ladder consists of a non-opioid. In newborns, paracetamol (also known as acetaminophen) is often used as first step. For infants older than 3 months of age a non-steroidal-anti-inflammatory drug (NSAID) such as Ibuprofen can be added. In preterm newborns, NSAIDS are used with caution because of the potential side effects. Ibuprofen and indomethacin are only used in order to close a patent ductus arteriosus. Next, a weak opioid such as Tramadol is added. However, in newborn children it is not recommended to use tramadol since it is only registered for children from 1 year of age onwards. The last step consists of strong opioids such as Fentanyl of Morphine. Both Fentanyl and Morphine are commonly used on the Neonatal Intensive Care Unit [29].

4.1. Paracetamol/acetaminophen

‘N-acetyl-para-aminophenol’ better known as paracetamol in Europe, or acetaminophen in the United States, is the most widely used drug for pain relief in newborns. Its use has been increased by the availability of an intravenous preparation. The mechanism of action is complex and includes the effects of both the peripheral (COX inhibition), and central (COX, serotonergic descending neuronal pathway, L-arginine/NO pathway and cannabinoid system) anti-nociception processes and so-called redox mechanism [80]. Debate exists about the primary site of action of paracetamol, which may be by inhibition of prostaglandin synthesis or through an active metabolite influencing cannabinoid receptors [81].

Paracetamol prevents peripheral sensitization and has an important central analgesic effect that is mediated through this activation of descending serotonergic pathways (Table 1). However, in newborn children the serotonergic system is more facilitatory instead of inhibitory [46]. The selectivity of serotonergic control of spinal somatosensation changes with postnatal age. Preclinical studies showed that in young animals the descending serotonergic control is non-selective and amplifies the saliency of low and high-threshold mechanical sensory inputs in the spinal cord. This occurs both by increasing neuronal activity and spatial receptive field sizes of dorsal horn neurons [82].

It has been shown that the use of intravenous acetaminophen reduces the use of morphine after surgery in neonates and is therefore the analgesic of first choice after surgery in neonatal life [4]. Major differences exist regarding the labelling of acetaminophen under the age of 1 year. When dosed adequately, acetaminophen is a poor procedural analgesic but it is very effective for mild-to-moderate pain with its additional morphine-sparing effects [83]. Moreover, in preterm born children a single dose during painful procedures showed no analgesic benefit [84], and it is generally believed that paracetamol is not an appropriate drug to treat procedural pain in newborns [85]. Interestingly, pre-emptive rectal paracetamol after assisted vaginal delivery was even associated with increased pain responses 2–3 days later during procedural pain [86]. Large studies on the pre-emptive use of paracetamol or on the potential long-term effects of paracetamol are needed [85]. Especially since previous studies showed potential associations and causal links between paracetamol exposure and neurobehavioral issues, increased incidence of atopy and reduced fertility [83].

4.2. Opioids

Opioids such as morphine, fentanyl, and remifentanil are commonly used in newborns. With respect to opioids, opioid receptors play a direct role in human neuronal development including neuronal migration, differentiation and maturation [87]. Opioid receptors are very important for normal brain development and therefore it is plausible that administration of high dosages of opioids during a period of rapid brain development will have adverse effects [87]. There are indications that opioids affect the dendritic architecture, neuronal density and μ receptor density [87]. Endogenous opioids β-endorphin and enkephalins (met- and leu-enkephalin) or analgesic drugs such as morphine or fentanyl can produce powerful analgesia by inhibiting the firing of nociceptive neurons in the dorsal horn of the spinal cord [31]. The μ-opioid receptor (OPRM1), the most potent target for analgesia, is distributed throughout the central nervous system with a high density in the dorsal horn (Table 1). Opioids activate the descending pathway from the brainstem by suppressing the inhibitory control of local GABAergic interneurons in the RVM and PAG, thereby activating projection neurons that in turn inhibit nociceptive transmission at the pain gate [31]. For an extensive review of nociceptive processing, the reader is referred to Refs. [48,52]. From studies in children with neonatal abstinence syndrome (NAS), we know that different polymorphisms in the μ-opioid receptor affect the incidence and severity of NAS [88]. Moreover, ontogeny plays an important role in the need for different dosing regimens of opioids [89]. The membrane ATP binding cassette efflux transporter P-glycoprotein expression at the meningeal blood-brain barrier is incomplete in the newborn period, but increases rapidly after birth and reaches adult levels in a few months of life. The limited expression in new-borns may allow drugs to be proportionally (brain/plasma ratio) higher in the brain. As a consequence, this may lead to an increased sensitivity to opioids, unrelated to the plasma concentration [89]. Moreover, based on animal studies we know that the endogenous opioid system undergoes crucial refinements in the descending pain modulatory pathway during postnatal development [42].

While intravenous morphine is administered to ventilated premature newborns in case of severe pain, it is not recommended to administer oral morphine to non-ventilated premature infants for procedural pain because of respiratory side effects without analgesic efficacy [5]. Next to that, morphine is not a suitable drug for short painful procedures, because of its pharmacological properties with a slow onset of action and a long half-life. Regarding preterm born ventilated children two large randomized controlled trials failed to show a positive effect of routine administration of morphine [90,91]. Studies on fentanyl and remifentanil are yet inconclusive [92]. Both drugs might be appropriate to treat severe painful procedural pain in newborns.

4.3. Other analgesic drugs

Methadone activates the opioid receptor similar to morphine, but it also blocks the N-methyl-D-aspartate (NMDA) receptor. Ketamine is another NMDA receptor antagonist. NMDA blockade is hypothesized to produce acute upregulation of the NMDA receptor, discontinuation of the NMDA receptor blocker is hypothesized to lead to excitotoxic neurotoxicity [87]. Not all NMDA antagonists induce apoptosis, however, and cell death can also occur during the NMDA blockade [87]. Therefore, the exact underlying mechanisms are not yet unravelled.

5. Conclusions

Treatment of pain in newborns, whether term or preterm born, remains a subject for improvement. Especially because the fear for negative short-term effects of pain such as increased morbidity and the fear for long-term effects with respect to neurocognition and pain processing. Even though research has made a big step towards understanding the development of the nociceptive system and the potential long-term effects of pain in newborns in the last decade, optimal and uniform treatment targets and algorithms are still needed.

In addition, the use of pre-emptive analgesia during the neonatal phase is thought to play an important role in the prevention of long-term side effects of pain. Future research should focus on the development of pain measurement techniques for clinical purposes. Moreover, research focussing on the assessment of maturational changes in the nociceptive system in a clinical setting is necessary. Finally, validation of translational measurement methods is needed in order to optimally study the effect of pain and analgesics in different stages of development. Age specific analgesic therapy based on postmenstrual age should be considered by incorporating information on the developmental stages of the nociceptive system in combination with knowledge from pharmacokinetic and –dynamic studies in newborns.

Practice points

- Pain in newborn children should be prevented or adequately treated due to negative short- and long-term consequences.
- The use of pre-emptive analgesia during pain in the neonatal phase is thought to play an important role in the prevention of long-term side effects of pain based on animal studies.
- Observational and behavioural pain scales have been implemented as the current best practice to assess pain in newborns and young children.
- Paracetamol or acetaminophen is a poor procedural analgesic but it is very effective for mild-to-moderate pain and has additional morphine-sparing effects in newborns.
- Morphine is not recommended for short painful procedures, because of its pharmacological properties with a slow onset of action and a long half-life.

Research directions

- Development of optimal and uniform treatment targets and algorithms focusing on targeted age specific analgesic therapy.
- Development of new pain measurement techniques for clinical purposes in newborns.
- Optimizing translation between clinical and preclinical pain measurement by utilizing similar techniques.
- Mechanism finding research in animal models is needed to assess maturational stage of treatment targets throughout development in order to further optimize treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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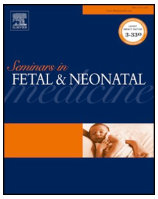

Non-pharmacological pain management in the neonatal intensive care unit: Managing neonatal pain without drugs

Oana Bucsea, Rebecca Pillai Riddell*

York University, Office of the Vice-President Research & Innovation, 509 Kaneff Tower, 4700 Keele Street, Toronto, ON, M3J 1P3, Canada

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ABSTRACT

Premature infants hospitalized after birth are exposed to repeated painful procedures as part of their routine medical care. Early neonatal exposure to unmanaged pain has been linked to numerous negative long-term outcomes, such as the development of pain hypersensitivity, detrimental psychological symptomology, and altered neurodevelopment. These findings emphasize the crucial role of pain management in neonatal care. The aim of this article is to give an overview of evidence-based non-pharmacological pain management techniques for hospitalized neonates. Research supporting the effectiveness of various proximal, distal, and procedural pain management methods in neonates will be presented. Additionally, understanding the larger biopsychosocial context of the infant that underpins the mechanisms of these pain management methods is essential. Therefore, two important models that inform non-pharmacological approaches to infant pain management (DIAPR-R [The Development of Infant Acute Pain Responding-Revised], Attachment Theory) will be discussed.

For infants born preterm, painful medical procedures are a routine part of their medical care. Research has demonstrated that approximately 7% of newborns are hospitalized after birth [1] and are subsequently exposed to repeated painful procedures. Previous research has found that neonates in NICUs experience an average of 7.5–17.3 daily painful procedures [2]. Approximately 70% of medical procedures carried out on neonates in the NICU are classified as painful [3]. Additionally, both preterm and term newborns requiring more intensive care, such as respiratory support, are exposed to an increased amount of acute procedures [4]. While it was previously believed that newborns did not feel pain [5], research findings have not only refuted this belief [6], but have also revealed that newborns' threshold for pain is likely lower than that of older infants and children [7] due to developing abilities to modulate pain both cognitively and physically. Moreover, preterm neonates' pain thresholds are seen as substantially lower than full-term newborns [7]. Given the ubiquitous nature of painful and invasive medical procedures in the NICU [8,9], the implications of repetitive painful procedures have also been studied in the literature.

Preterm newborns' length of NICU stay and amount of early exposure to painful procedures are predictive of detrimental psychological symptoms, such as somatization and internalizing symptoms, during their preschool and school years [10,11]. Early neonatal exposure to unmanaged pain has also been linked to altered neurodevelopmental outcomes in school aged children, such as thinner cortical regions, predominantly those associated with the frontal and parietal lobes [12]. In addition to undermanaged acute pain leading to highly distressing procedures for newborns, research has linked early pain exposure with multiple adverse long-term effects, relating to both subsequent pain reactivity and mental health outcomes. For instance, infants demonstrate a subsequent hypersensitivity to pain with early exposure to painful procedures [13,14]. This also leads to higher distress reactivity perceiving subsequent non-noxious procedures, such as diaper changes, as painful [15].

It is unequivocal that neonates are exposed to an abundance of iatrogenically painful procedures during an exquisitely sensitive period of development, which results in long-term implications that scientists and clinicians are only beginning to understand. Pain management is a critical factor to understand in neonatal care. This article will discuss pain management strategies that focus on cognitive, behavioural and contextual approaches. However, while pain management strategies will be presented, understanding the larger biopsychosocial context of the infant that helps to explain the mechanisms of these approaches is of primary importance. Two important models that should inform nonpharmacological approaches to infant pain management (DIAPR-R [The Development of Infant Acute Pain Responding-Revised], Attachment Theory) will be discussed to set a foundation.

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* Corresponding author.
E-mail address: rpr@yorku.ca (R. Pillai Riddell).
URL: http://www.yorku.ca/ouchlab (R. Pillai Riddell).
@drbeccapr (R. Pillai Riddell)

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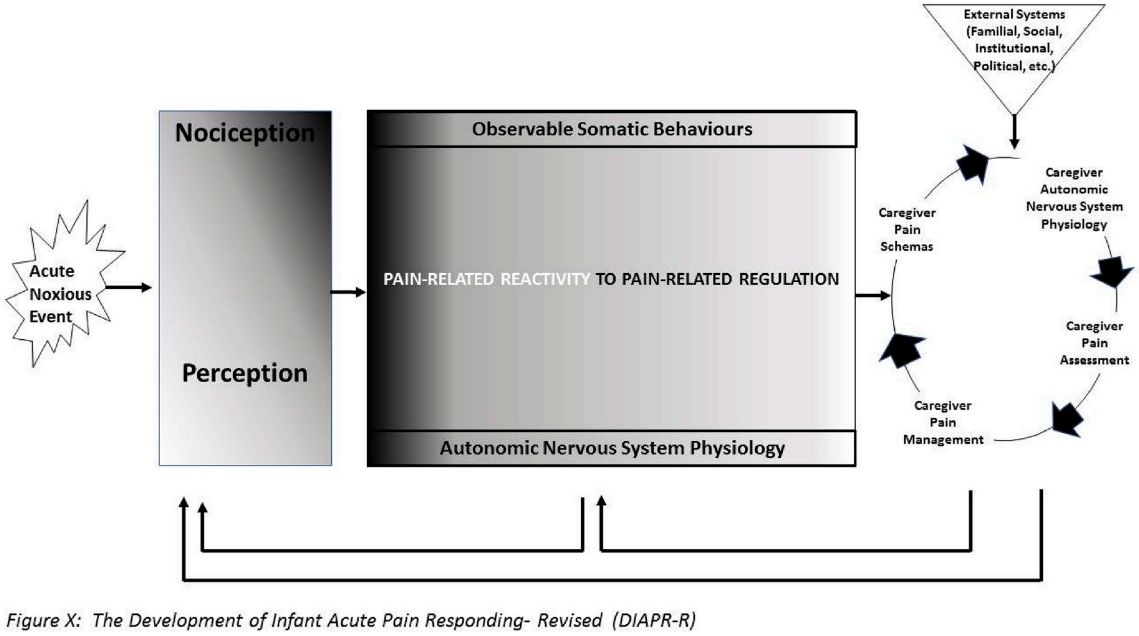
External Systems (Familial, Social, Institutional, Political, etc.)
Nociception
Perception
Acute Noxious Event
Observable Somatic Behaviours
PAIN-RELATED REACTIVITY TO PAIN-RELATED REGULATION
Autonomic Nervous System Physiology
Caregiver Pain Schemas
Caregiver Autonomic Nervous System Physiology
Caregiver Pain Assessment
Caregiver Pain Management
Figure X: The Development of Infant Acute Pain Responding- Revised (DIAPR-R)

Fig. 1. The Development of Infant Acute Pain Responses- Revised (Pillai Riddell 2018, as cited in Goubert, Pillai Riddell, Simons and Borsook, in press).

1. A biopsychosocial model of infant acute pain: the DIAPR-R model

In order to effectively manage infant acute pain, the underlying biological, cognitive, emotional, and social aspects of the pain experience must be understood. Currently, there is only one biopsychosocial model designed to specifically understand infant acute pain from a biopsychosocial perspective - the DIAPR-R [[16], See Fig. 1]. While based on an extensive program of longitudinal research with the OUCH Cohort (www.yorku.ca/ouchlab) with healthy infants over the first year of life, the relevance to the preterm child is strong. A few key features of the DIAPR-R model deserve highlighting. First, similar to the first version of the model [17], it purports that infants are biologically predisposed to seek the help of others in times of distress. Lacking the physical and cognitive capacity to protect themselves from danger, during periods of distress (such as pain), infant responding must be taken into the context of caregiving. New to the model, based on collaborative work with a neurophysiological research group (Fitzgerald lab, University College London), the model took a stronger attempt to speculate and present the nuances of the biological processing of the event.

Immediately following the painful event, the DIAPR-R model illustrates the progression of the pain response, from the initial **nociception** (marked by the cascade of events from the peripheral nociceptor to the first afferent signals in the primary and secondary somatosensory cortex), to the **perception** of the painful stimulus (characterized by the widespread cortical activation in areas such as the prefrontal cortex, anterior cingulate cortex, insular cortex, and the amygdala), which are associated with the process of making sense of the initial response in the somatosensory cortex [18]. These initial processes combine to inform the infants' **pain-related reactivity** response, which subsequently transitions into a **pain-related regulation** response as the child returns to baseline distress levels. This sequence from nociception and perception to pain-related reactivity followed by pain-related regulation is additionally impacted by the caregiver context, such as the caregivers' cognitions (e.g., pain schemas and assessments), as well as their responses (e.g., caregivers' ANS physiological responses and their engagement in pain management strategies). As aforementioned, the caregiver context is particularly important in neonates, due to their inability to engage in self-directed regulation strategies, thus making it necessary for them to rely on sources of external distress regulation [19,20]. Moreover, on a broad level, the DIAPR-R model also depicts the infants' larger systemic influences (e.g., culture) as exerting an effect on their pain response via the caregiver [21]. Importantly, the model uses feedback loops to demonstrate the mechanisms via which the caregiver context and the non-immediate pain response feedback on the nociception and perception of pain.

The new DIAPR-R model borrows heavily on a fundamental principle from decades of work in developmental psychology on the Attachment System. Initially formulated by Bowlby [22,23] and operationalized by Ainsworth et al. [24] and Main & Solomon [25], the attachment relationship, i.e. the way in which a child has been socialized by a caregiver throughout early childhood regarding how to involve them to regulate distress, is critical to integrate when understanding psychological (cognitive, behavioural, contextual) perspectives to infant pain management. The next section provides more detail in understanding infant pain within a caregiver context.

2. Infant acute pain and attachment: the importance of the caregiver context

Grounded in Attachment Theory [22,23], the DIAPR-R model emphasizes the caregiver context of infant pain as fundamental to understanding its response. Over the first year of life infants are biologically predisposed to respond in ways that are predicated on having a caregiver present. From an attachment perspective, it is purported that a newborn is born able to signal distress (e.g., crying) in order to achieve physical proximity to their caregiver and alert the caregiver to engage in distress-reducing or mitigating intervention. Alternatively, it is also theorized that parents have an innate system activated by infants' distress signals, which in turn prompts them to respond in a soothing manner that will help regulate the infants' negative affect [26]. Decades of developmental psychology research have demonstrated that repeated caregiver-child interactions in distressing situations subsequently predict children's behaviour in distressing situations, which are operationalized as attachment categorizations (specifically secure, avoidant, resistant, and disorganized). While a detailed primer on Attachment Theory is beyond the scope of the chapter, the following descriptions are offered as a quick heuristic due to its relevance to understanding not only infant pain management but infant pain assessment [27], as so much of assessing the need and the impact of pain management is based on overt signalling. Secure infants have learned to react vigorously to distress and are more easily regulated post-distress by a caregiver whom they have learned is generally responsive to their distress. Avoidant infants have learned to mute overt distress and attempt to avoid a caregiver because they have learned to be generally rejecting during distress. Resistant infants have learned to amplify and sustain distress signalling to help ensure proximity due to learning their caregiver can be inconsistently responsive. Finally, disorganized infants tend to respond in ways that do not appear to be organized ways of interacting with a caregiver (e.g. a complete lack of behavioural response to distress). Disorganization is often based on having interactions, during distressing situation, with their caregiver where the caregiver is perceived as frightening or otherwise atypical. Disorganization as an outcome should be of particular concern when understanding preterm infants in pain, given the allostatic stress load of repetitive painful procedures in a constrained parental caregiving context. Longitudinal research has suggested NICU infants have a higher chance of attachment disorganization [28]. Moreover, positive caregiver-infant interactions have been demonstrated to exert a buffering effect on the relationships between early neonatal pain exposure in preterm infants and subsequent cognitive functioning and mental health outcomes [29,30].

3. Importance of the caregiver context in neonatal pain management

The above findings point to the importance of caregiver inclusion in the implementation of pain management techniques in hospital settings. This is supported by previous research indicating a positive link between maternal involvement in hospitalized infants' care and newborns' levels of stress and pain [31]. Furthermore, NICU nurses have previously pointed to their heavy workload and the lack of maternal presence in the NICU during infants' medical procedures as some of the main challenges for failing to engage in non-pharmacological pain management strategies, such as skin-to-skin contact [32]. In contrast, 87% of parents of NICU infants have reported a desire to be involved in their children's pain management and, out of those who participated in a study examining attitudes to maternal care in the NICU, 80% indicated it was a positive experience and 90% would wish to be included again [33].

4. Non-pharmacological pain management techniques in neonates

Previous pain management models, such as the “5P” approach [34], which denotes procedural, physical, pharmacological, psychological, and process pain management interventions, have been proven crucial in directing pain management efforts for older infants and children. However, many techniques traditionally used in older infants and children are not appropriate for preterm neonates. For example, distraction has been posited to be more effective in older infants due to the immature motor and cognitive capacities at birth [35]. Moreover, longitudinal work with term infants over vaccinations in the first year of life has suggested that younger infants keep their eyes closed longer, posited to reflect sensory overwhelm and a greater dependence on caregiving [36,37].

Rather than organize in traditional groupings such as the 5P's, owing to the unique context of infancy, the article will proceed based on how the strategies are enacted with neonates, namely proximal, distal, and procedural methods of what is mostly acute pain. However, it is important to note that many of the below strategies reflect attachment principles of proximity to caregiver and increasing feelings of safety/secureness and would be helpful regardless of whether the stressor is painful or not.

A few notes regarding the following review: due to preterm neonates comprising a large proportion of hospitalized newborns in NICUs, the bulk of the data presented below will originate from research with preterm, as opposed to full term, neonates. Therefore, the nature of the sample (preterm versus full term) will only be specified if a study is based on full term neonates. Moreover, whenever possible, the effectiveness of pain management methods on reducing neonates' pain-related reactivity (earliest reactions after the painful stimulus) versus regulation (later reactions that occur after the initial painful response) will be specified [38]. Although interrelated, the distinction of these two phases is warranted, as research has suggested that non-pharmacological pain management interventions may be more related to infants' pain levels in the regulatory phase, rather than the reactivity phase [17]. Finally, readers are drawn to a recent Cochrane Review that directly reviews the literature on 22 different non-pharmacological strategies for infant and young child procedural pain [38].

4.1. Proximal pain management methods

Proximal methods of pain management support newborns to achieve baseline states post-painful procedure and alleviate pain by providing soothing tactile stimuli before, during, and/or after the painful procedure. According to the Gate Control Theory [39], it may be that the signals elicited by the soothing stimuli travel up ascending pathways, inhibiting the nociceptive signals created by the noxious event, through endogenous mechanisms located along the spino-thalamic tract [40].

Pain management techniques that can be encompassed in this category include skin-to-skin contact (also known as kangaroo care), facilitated tucking (containing an infant by hand-hugging), swaddling (containing an infant with a blanket), sucking-related strategies (e.g., non-nutritive sucking on a pacifier or finger), rocking, and breastfeeding. Non-nutritive sucking, swaddling/tucking, and rocking/holding were determined to be promising pain management interventions for full-term neonates [38]. However, age differences emerged, with non-nutritive sucking failing to relieve preterm neonates pain' reactivity. Swaddling/tucking interventions and touch/massage showed promise for preterm infants [38]. Hartley, Miller, and Gephart [41] conducted an additional review that supported these results, demonstrating the effectiveness of facilitated tucking at reducing pain in preterm newborns. The results of a randomized controlled trial on the effects of swaddling on acute pain in preterm neonates also revealed analgesic effects, with the swaddled group exhibiting lower pain scores and faster returns to baseline following a blood sampling procedure [42].

Furthermore, Pillai Riddell et al. [38] also concluded that sucking-related interventions and facilitated tucking/swaddling were shown to be effective at alleviating pain in the reactivity stage, while sucking-related interventions and rocking/holding demonstrated effectiveness during the regulation stage. The above findings are bolstered by a second review examining the combined effects of non-nutritive sucking on pain responses in neonates and older infants up to 4 months old. In this review, Taddio and colleagues [43] showed non-nutritive sucking to be effective in reducing infant pain-related distress.

Skin-to-skin care and co-bedding. Johnston et al. [44] concluded that skin-to-skin care is more beneficial at relieving both behavioural and physiological indicators of pain than standard care. Although the pain reduction effects of skin-to-skin care have been demonstrated, nurses have stated multiple challenges precluding them from providing this care to neonates in NICUs, such as heavy workload. Mothers' presence during acute procedures in order to provide skin-to-skin contact for their children was provided as a potential solution to this issue [32]. Another pain-management intervention related to proximity is co-bedding, the action of placing multiple newborns in a singular incubator. Co-bedding has been linked to a better regulated stress response following an acute procedure in neonates, as indicated by reduced cortisol levels and faster returns to baseline physiology [45].

Breastfeeding. Shah, Herbozo, Aliwalas, and Shah [46] led a systematic review on the effects of breastfeeding on crying time and pain scores in full-term newborns and results revealed its effectiveness over other positioning interventions (e.g, swaddling; placing the neonate in a crib), placebos, and standard care. These findings were bolstered by another systematic review conducted in 2015 on the benefits of breastfeeding for analgesic purposes [47]. Fallah, Naserzadeh, Ferdosian, and Binesh [48] demonstrated more effective analgesia in breastfeeding compared to kangaroo care and swaddling in term neonates. Interestingly, providing newborn babies with breast milk via a syringe did not lead to the same analgesic effects as breastfeeding, potentially due to the latter reducing pain-related distress via multiple mechanisms due to the combination of holding- and sucking-related interventions with ingestion of a sweet-tasting substance [34]. This further points to the importance of including mothers in pain management implementations.

4.2. *Distal pain management methods*

Distal pain management interventions involve modifying the neonates' environment to achieve a diminished pain response and pain-related distress. This category includes strategies such as controlling the noise, lighting, and smells in the NICU.

Odours. Pillai Riddell et al. [38] found that environmental modifications, such as introducing familiar odours, were effective in relieving newborns' pain in the regulation phase.

Light. Light intensity has been shown to have negative effects on neonates in NICUs, while intermittent lighting has been associated with reductions in heart rate, strengthened biological rhythm, and better sleep quality and nutrition [49]. This concept has also been applied to research examining the potential analgesic effects of low lighting. For instance, a study exploring the effects of covering newborns' eyes during a painful procedure revealed a significant reduction in infants' behavioural pain responses solely when the pain intervention was executed after the procedure, not during [50]. However, reductions in the physiological domains of pain, such as heart rate and SaO_2 levels, were not observed; therefore, further studies examining the analgesic effects of light in NICUs are warranted.

Sound/music therapy. Previous studies have attempted to analyze the analgesic effects of sounds/music therapy in NICUs, posited to reduce pain by decreasing infants' state of arousal and pain-related behavioural responses [51]. However, studies have yielded mixed results. One type of sound therapy that has demonstrated analgesic qualities in both preterm and full-term neonates has been exposure to the mother's voice [52,53]. Additionally, listening to classical music was shown to be effective in reducing pain responses during routine heel lances [54]. Alternatively, Badr et al. [55] discovered that exposing neonates to lullabies or to music their mothers listened to during pregnancy had a positive impact on children's behavioural measures of pain, but not physiological. Other interventions, such as exposure to intrauterine sounds such as heart rate in an attempt to reduce pain reactivity have also shown promise [56].

4.3. *Procedural pain management methods*

It is important to remind readers that avoiding unnecessary painful procedures should always be the first line of pain management. However, when medically necessary, pain management implementations can also aim to achieve pain reduction by targeting and refining the medical procedure itself. Examples of procedural pain management techniques incorporated in this classification are choosing appropriate injection sites, sequencing vaccines suitably in an attempt to reduce their additive pain in order of least painful to most painful, and using aspiration versus no aspirations during vaccines. For instance, heel lances are the most commonly used procedures in NICUs for blood sampling [57]. However, a systematic review on heel lance versus venepuncture for neonate blood sampling concluded that venepuncture yield lower pain scores on numerous validated measures of pain in full-term neonates [58]. Moreover, research analyzing the analgesic effects of adding upper limb massage to the vaccination procedure, i.e. prior to administering venepuncture, in a sample of preterm and full-term neonates has revealed lower pain scores in those who received the massage intervention [59].

A review that combined results from newborns with infants up to 6 months old determined that, when administering multiple vaccines, injecting the most painful one last produces lower overall distress in all ages [43].

4.4. *Additive effects of combined pain management methods*

As the research on infant pain matures, the use of a no pain management control group has evolved to become unacceptable. Some studies have thus analysed the additive analgesic effects of multiple combined pain management techniques to find more optimal ways of pain management, which will be reviewed next.

Research examining the combined effects of non-nutritive sucking and sucrose indicated an additive analgesic effect of non-nutritive sucking compared to sucrose alone. Furthermore, tucking/swaddling combined with non-nutritive sucking was superior compared to non-nutritive sucking alone [38]. Combined holding-related implementations (consisting of either cuddling and back-patting or swaddling, side-lying, swinging, sucking, and shushing) administered after the painful procedure have also been shown to reduce distress in newborns and infants up to 4 months old [43]. Finally, newborns displayed fewer pain-related behaviours (i.e., grimacing, squirming, limb and truck extensions) when exposed to a combination of non-nutritive sucking, facilitated tucking, and sucrose than either of these interventions alone [60].

Compared to the combined effects of facilitated tucking, non-nutritive sucking, and oral glucose, the addition of music therapy has been linked to neonates displaying more stable physiological and behavioural responses, allowing nurses to complete the required routine procedures more efficiently [61]. Further support for the benefits of music on pain-related distress emerged from Qiu et al. [62], who examined the analgesic effects of Combined Music and Touch (CMT) intervention and concluded its effectiveness at reducing neonates' pain response as measured by the PIPP. Furthermore, Shah, Kadage, and Sinn [63] determined that, although the analgesic benefits of music therapy were comparable to those of sucrose in full term neonates, the combination of the two yielded the greatest level of pain relief.

Shah et al. [47] revealed an additive effect of breastfeeding when combined with a pharmacological pain management implementation, such as a topical anaesthetic. In NICUs where expressed breast milk was considered standard care, combining this procedure with skin-to-skin mother care was shown to be more beneficial at reducing neonates' pain [64].

Overall, it appears that combining certain pain management techniques may have stronger analgesic effects compared to administering individual techniques.

5. Future directions

Further research is warranted to bolster the support for the current review, particularly randomized controlled trials on adequately-powered samples that use methodological standards for interventional research. More fundamentally, current pain assessment (the bedrock of optimal pain management) is currently predicated on high levels of convergence of biological and behavioural measures of pain. However, there have been important challenges to the supposition. For instance, Slater et al. [65] revealed that, although oral sucrose was effective at reducing newborns' behavioural expressions of pain, it had no analgesic effect on the underlying nociceptive brain activity or spinal cord circuits. Jones et al. [66] have found that in high stress contexts, biological and behavioural relationships are not seen (in contrary to strong relationships when infants show evidence of lower stress situations). Two other papers [50,55] suggested analgesic effects solely on pain-related behavioural expressions and not on the underlying physiology. Finally, it is important to recognize that there is large variability in infant pain responding. Basing the efficacy or effectiveness of any infant pain intervention by simplistically comparing group means without any disaggregation of this variability will not result in understanding the true treatment effects of an intervention [67].

6. Concluding notes

Given the large number of pain management techniques and the exponentially large number of potential combinations, it is impossible for any review to touch upon all these combinations. Thus, clinicians are likely best served by keeping in mind key principles of neonatal pain management as reviewed such as avoiding procedures, providing soothing tactile stimulation, helping an infant to feel contained, encouraging proximity to a caregiver before, during, and after a procedure and using pharmacological interventions that may be more apt to block or moderate nociception. Moreover, scientists are encouraged to look at challenges to current study methodologies to provide better data regarding the efficacy of different pain management techniques for infants.

Practice Points

- Hospitalized preterm neonates are frequently exposed to painful medical procedures
- Early neonatal pain exposure is linked to detrimental long-term outcomes
- Pain management methods are crucial in neonatal care
- Non-pharmacological pain management (proximal, distal, and procedural) methods have shown effectiveness at reducing neonates' pain responses
- Combining certain pain management techniques may have stronger analgesic effects compared to administering individual techniques

Research Directions

- Randomized controlled trials on adequately-powered samples analyzing the efficiency and effectiveness of pain management methods are needed
- Differentially examining the analgesic effects of pain management methods on infants' behavioural versus physiological pain responses must be conducted
- Acknowledging the large variability in infant pain responding in order to uncover the true treatment effects of interventions

Conflict of interest

The authors have no conflicts of interest to disclose.

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Managing neonatal pain in the era of non-invasive respiratory support

Manon Tauzin[a], Xavier Durrmeyer[a,b,c,*]

[a] Neonatal Intensive Care Unit, Centre Hospitalier Intercommunal de Créteil, Créteil, France
[b] Université Paris Est Créteil, Faculté de Médecine de Créteil, IMRB, GRC CARMAS, Créteil, France
[c] INSERM, UMR1153, Obstetrical, Perinatal and Paediatric Epidemiology (Epopé) Team, Epidemiology and Biostatistics Sorbonne, Paris Descartes University, Paris, France

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ABSTRACT

Non-invasive ventilation is currently the preferred respiratory support for premature infants with respiratory distress. The lung-protective effects of non-invasive ventilation should however not prompt disregard for the possible pain and discomfort it can generate. Non-pharmacological interventions should be used in all premature infants, regardless of their respiratory support, and are not detailed in this review. This review includes currently available evidence and gaps in knowledge regarding three aspects of pain management in premature infants receiving non-invasive ventilation: optimisation of non-invasive ventilation especially through the choice of positive pressure source, appropriate interface and synchronisation; sedative or analgesic drug use for strategies aiming at administering surfactant with reduction or avoidance of tracheal ventilation; risks and benefits of some analgesic and/or sedative drugs used to treat or prevent prolonged pain and discomfort during non-invasive ventilation. In spite of limited robust evidence, this overview should trigger caregivers' reflections on their daily practice.

1. Introduction

Non-invasive ventilation (NIV) is preferred to invasive ventilation in premature neonates as it is associated with increased survival without bronchopulmonary dysplasia [1]. Unlike patients from other age groups, premature neonates can thus receive uninterrupted NIV during their hospital stay for prolonged periods that can last for weeks or even months for the most immature infants [2]. But NIV can cause discomfort or even pain, especially through nasal injury [3], which can compromise the efficacy of NIV itself. In addition, optimising the comfort and pain management of these babies is mandatory, not only to improve the efficacy and tolerance of their respiratory support, but also to preserve their later neurodevelopmental outcome [4]. Non-pharmacological strategies to reduce pain and improve comfort in the neonatal intensive care unit (NICU) have been reviewed elsewhere [5] and should be implemented for babies receiving NIV. The first part of this review will specifically focus on the devices and interfaces used during NIV for premature infants and their impact on comfort and pain.

In order to further reduce tracheal ventilation, several strategies have been proposed to deliver surfactant. First, the "Intubation-surfactant administration – immediate extubation" (INSURE) technique has been used for several years and requires specific premedications to allow rapid extubation. Second, strategies to deliver surfactant without endotracheal intubation have recently emerged including "less invasive surfactant administration" (LISA) or "minimally invasive surfactant treatment" (MIST) and laryngeal mask use [6]. These techniques probably have a positive effect on respiratory morbidity [6,7], and are rapidly spreading in some countries [8]. However, sedation or analgesia are rarely used to perform these procedures [8]. Since LISA or MIST require laryngoscopy, a known painful procedure, their performance without sedation and/or analgesia might be considered as a regress compared to endotracheal intubation, for which such treatments are recommended [9] and usually given [10]. Thus, the second part of this review will provide a synthesis on the efficacy and tolerance of premedication regimens used for surfactant administration using the INSURE technique, LISA/MIST techniques or laryngeal mask.

Finally, the daily care of these babies is extremely challenging since their respiratory disease and immature central respiratory command expose them to frequent apnoea and desaturations. Therefore, any intervention aimed at improving their comfort should avoid respiratory depression, which makes difficult the use of most sedative, analgesic or anaesthetic drugs. Thus, the last part of this review will focus on pharmacological treatment in infants receiving NIV.

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[*] Corresponding author. Pédiatrie et réanimation néonatales, CHI Créteil, 40 avenue de Verdun, 94000, Créteil, France.
E-mail addresses: manon.tauzin@chicreteil.fr (M. Tauzin), xavier.durrmeyer@chicreteil.fr (X. Durrmeyer).

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2. Improving comfort during non-invasive respiratory support

2.1. Role of NIV system: continuous positive airway pressure (CPAP) versus heated and humidified high flow nasal cannula (HFNC)

Several randomised controlled trials have compared CPAP with HFNC in premature infants with respiratory distress to assess their respective efficacy in treating respiratory distress syndrome after birth or in preventing extubation failure [11]. The systematic review and meta-analysis performed by Wilkinson et al. did not find any obvious difference in studied outcomes between HFNC and alternative NIV strategies, except for a reduction in nasal trauma associated with HFNC (risk difference (RD) −0.14, 95% CI -0.20 to −0.08) [11]. However, the alternative NIV strategies included various systems, devices and interfaces that complicate the interpretation of results.

A systematic review assessing nasal injury during NIV in premature infants found incidences ranging from 20% to 100% and confirmed the reduction in nasal injury with the use of HFNC as compared to CPAP (RD - 0.14, 95%CI -0.17 to −0.10), although important heterogeneity between studies was noted [3].

Two studies have more specifically assessed infants' comfort and/or pain as a primary outcome by comparing HFNC and CPAP [12,13]. In a cross-over study, Klingenberg et al. assessed pain using a cumulative EDIN pain score [14] (sum of 3 assessments) in 20 premature infants (mean (SD) gestational age, 29.3 (1.7) weeks; median (IQR) postnatal age, 6 (4–10) days) who were assigned to two 24 h periods of ventilation with variable flow CPAP or HFNC in a random order [12]. The cumulative EDIN score was around 11 in both groups (meaning a mean score below 4 for each of the three assessments), without any significant difference between groups, which suggests that both ventilatory devices resulted in acceptable comfort in this study. Since the sample size calculation was based on the assumption that the cumulative EDIN score in the CPAP group would be 16 and that a 25% reduction (i.e. EDIN score = 12) would be observed in the HFNC group, it is possible that the study was underpowered, as mentioned by the authors [12].

An observational cross-sectional study assessed pain using the premature infant pain profile (PIPP) [15] in 60 subjects supported with CPAP or HFNC [13]. In this study, infants had a median gestational age of 32 weeks and a median postnatal age of 5–6 days. The PIPP score was calculated by trained nurses who watched videos (45 s) and who were not informed of the nature of the study. In this study, Osman et al. reported a significant decrease in PIPP scores in the HFNC group versus the CPAP group (respectively 4 (2–6) and 10 (7–12), $p = 0.01$). No infant in the HFNC group had a PIPP score > 12 (the admitted threshold for severe pain) versus 5/37 (13.5%) in the CPAP group ($p = 0.03$). It is however interesting to note that 7/23 (30.4%) infants from the HFNC group and 19/37 (51.4%) infants from the CPAP group had scores between 6 and 12, which indicates mild to moderate pain. Although their study had limitations, Osman et al. objectively demonstrated the possible painful effect of these two non-invasive devices in premature infants, in the absence of other painful procedure or nasal injury (non-inclusion criteria) [13].

In summary, the evidence is not sufficient to recommend HFNC use over CPAP, however it should be strongly considered in babies at risk of nasal injury and in babies showing signs of discomfort while receiving CPAP.

2.2. Role of NIV interface

In addition to the elevated number of devices available to provide NIV, there is an even larger number of interfaces to be placed on the infants' face [16]. If binasal prongs are more effective than single nasal/nasopharyngeal prongs in reducing the rate of re-intubation [17], no consensus exists to date concerning the type of binasal prongs or mask that should be preferentially used. RAM nasal cannulae have also been proposed as an alternative to binasal prongs or masks [18]. When choosing a specific interface for an infant, caregivers should consider both the efficacy and the tolerance of the selected device. Since the status of these infants is rapidly changing, it seems misleading to think that a specific interface will meet the needs for all babies. However, some studies have specifically assessed the comfort of different interfaces used for NIV in premature infants.

In a secondary analysis of an open labelled, multi-centre, randomised, controlled trial, Khan et al. assessed nasal injuries and pain using the N-PASS scale [19] in 170 premature infants who received either Jet CPAP with dedicated prongs or bubble CPAP with two types of short binasal prongs: Fisher and Paykel's prongs (Healthcare, New Zealand) or Hudson prongs (Hudson Respiratory Care Inc., Temecula, California, USA) [20]. Nasal injury was observed in 36/80 (45%) infants from the Jet CPAP group *versus* 67/90 (74%) for the bubble CPAP group (relative risk 0.6, 95% CI 0.5 to 0.8). Neonates in the Jet CPAP group had significantly lower average (median (IQR): 3 (8, 13) vs. 4 (8, 14); $p = 0.04$) as well as maximum N-PASS pain score (median (IQR): 4 (8, 14) vs. 5 (13, 16); $p = 0.01$) in comparison to the bubble CPAP group.

A systematic review assessed different strategies to prevent or reduce nasal injury in premature infants receiving NIV [3]. Pooled analysis identified the use of nasal barrier dressing (RD -0.12, 95%CI -0.20 to −0.04), as well as the use of nasal mask rather than binasal prongs (risk ratio 0.80, 95%CI 0.64 to 1.00) as potentially useful strategies to prevent nasal injury [3]. In line with these conclusions, a randomised controlled trial demonstrated that the use of nasal barrier dressing significantly reduced nasal injury during binasal NIV: nasal injury was observed in 18/53 (34%) infants in the barrier group vs 31/55 (56%) in the no barrier group ($p = 0.02$) [21]. The reduction in severe nasal injury with nasal mask was also reported in another meta-analysis (risk ratio 0.41, 95% CI 0.24 to 0.72), in addition to a significant reduction in CPAP failure (risk ratio 0.63, 95% CI 0.45 to 0.88) as compared to binasal prongs [22].

The RAM cannula was assessed in a limited number of studies. In a single-centre prospective observational study, it was used in infants receiving CPAP or nasal intermittent positive pressure ventilation (NIPPV) with skin breakdown or discomfort/agitation [18]. Although comfort or pain was not assessed in this study, Nzegwu et al. reported that there were no new instances of nasal breakdown or injury with RAM nasal cannula use [18]. In another prospective observational study, the rate of nasal injury was significantly decreased with the use of RAM cannula, as compared to a historical control group: 3/36 (8%) in the RAM cannula group vs 19/36 (53%) in the control group ($p < 0.01$) [23].

In summary, nasal mask use probably reduces the risk of nasal injury without compromising CPAP. However, the use of a single interface is rarely feasible in practice and alternating interfaces may be helpful to change sites of constant pressure on the infant's face [3]. When using binasal prongs, the use of a nasal barrier dressing should be strongly considered. The use of RAM cannula might also be considered, provided that its efficacy is considered acceptable as compared to other interfaces.

2.3. Neurally adjusted ventilatory assist (NAVA)

NAVA is a ventilatory mode using the diaphragm electrical activity to deliver synchronised and proportional inspiratory pressure invasively or non-invasively [24]. In the pediatric ICU, mechanical ventilation with NAVA led to a reduction in sedation after excluding postoperative patients, as compared to conventional ventilation [25].

However in neonates, a randomised controlled trial using duration of ventilation as primary outcome found no difference in the cumulative dose of opiates used during conventional ventilation or invasive NAVA [26].

NIV with NAVA has been assessed in some studies, but none specifically assessed comfort or pain. In a crossover trial including 15 infants (median (IQR) GA, 27 + 1 (26 + 0–28 + 2) weeks; median (IQR) postnatal age, 25 (17.5–32) days), Lee et al. showed a significant improvement in synchronisation with NIV-NAVA as compared to NIV-pressure support (asynchrony index 19.7% *vs* 73.9%, $p < 0.001$) [27], which probably contributed to infants' comfort. In a pilot crossover trial conducted in seven infants (median (IQR) GA, 26.6 (25.2–26.6) weeks; median (IQR) postnatal age, 23 (19.5–36.5) days), Gibu et al. observed a significant reduction in the frequency of desaturations (−42 ± 12%, $p < 0.006$), the duration of desaturations (−33 ± 10%, $p < 0.01$), the infant movements (−42 ± 9%, $p < 0.01$) and caretaker movements (−29 ± 8%, $p < 0.01$) [28]. Altogether, these parameters might be a proxy for the infants' comfort that was not directly assessed in this study.

3. Use of analgesic and sedatives for surfactant administration without subsequent invasive ventilation

3.1. *Intubation - surfactant administration - extubation (INSURE) technique*

The INSURE technique aims at reducing the duration of invasive ventilation and is associated with less need for mechanical ventilation, lower incidence of BPD and fewer air leak syndromes [29]. Premedications used during the procedure have been reviewed in 2013 and the authors concluded that short-acting opioids (especially remifentanil) or propofol were suitable candidates, although evidence was insufficient to recommend a specific dosing or protocol [30]. Since then, a prospective study with remifentanil (cumulative doses ranging from 1 to 5 µg/kg) was prematurely interrupted because of poor sedation and frequent chest wall rigidity [31]. A dose-finding study on propofol as premedication before the INSURE procedure proved the feasibility of a titration strategy and recommended relatively low initial doses (0.7–1.4 mg/kg) with subsequent up-titration [32].

3.2. *LISA/MIST techniques*

LISA/MIST techniques are associated with reduced BPD as compared to invasive surfactant administration methods [7]. However, most published randomised trials did not use any premedication prior to laryngoscopy [2,33–36], although conscious laryngoscopy is undoubtedly painful and associated with adverse physiological reactions such as increased intracranial pressure [9]. The main characteristics and findings of clinical studies on LISA/MIST with or without sedation/analgesia are summarised in Table 1. Most studies using analgesia or sedation recruited infants around 29 weeks GA [37–40]. When compared to studies without premedication in the same GA group [33,36], the frequency of any mechanical ventilation before 72 h of life appeared higher. In addition, desaturations were very common in studies that used analgesic or sedative drugs (Table 1).

To date, one randomised controlled trial has compared 1 mg/kg intravenous propofol to no premedication before LISA, using the Comfortneo [41] score < 14 as primary outcome [39]. In this study Dekker *at al.* found a significant decrease in the rate of infants with a Comfortneo score < 14 in the propofol group as compared to the control (no premedication) group: 8/36 (22%) *vs* 32/42 (76%), respectively ($p < 0.001$) [39]. However, this improvement in pain control was at the expense of increased respiratory support (NIPPV) (93% *vs* 47%, $p < 0.001$) and more frequent desaturations during the procedure (91% *vs* 69%, $p = 0.023$) in the sedated group, without significant increase in the intubation rate within 24 h (24% vs 17%, $p = 0.58$).

Two previous observational studies already suggested the suitability of low dose propofol to perform LISA/MIST [38,40] and another observational study found a relatively high rate of subsequent intubation with the use of ketamine [37].

In summary, although low dose propofol seems promising, more research is required to find an optimal premedication regimen to

Table 1
Summary of studies on LISA/MIST with or without analgesia/sedation.

	Clinical trials without systematic analgesia/sedation					Clinical trials with analgesia/sedation			
Publication's reference	[34]	[35]	[36]	[33]	[2]	[38]	[40]	[37]	[39]
Study's design	RCT	RCT	RCT	RCT	RCT	Retrospective study	Retrospective study	Prospective study	RCT
Population Mean GA (weeks), N	27.6 n = 108	28.0 n = 100	29.6 n = 66	29.1 n = 46	25.3 n = 107	29.0 n = 23	29.5 n = 35	30.0 n = 29	29.0 n = 42
Premedication	At the discretion	None	Atropine	Not specified *Probably none*	Not specified *Probably none*	Propofol 1 mg/kg	Propofol titration 0.5 mg/kg	Atropine Kétamine titration 0.5 mg/kg	Propofol 1 mg/kg
MV < 72 h	28%	30%	19%	17%	47%	35%	34%	41%	24%[a]
Tolerance	Nadir SpO_2 80 (70–87)	17% bradycardia and desat	4.5% desat	Not detailed	56% $SpO_2 < 80\%$	100% $SpO_2 < 80\%$	100% $SpO_2 < 85\%$	58% $SpO_2 < 80\%$ > 60s	91% $SpO_2 < 85\%$ 33% MABP < GA

Abbreviations: RCT, randomised controlled trial; GA, gestational age; MV, mechanical ventilation; desat, desaturation; MABP, mean arterial blood pressure.

[a] Use of MV within 24 h of the procedure.

perform LISA/MIST and this research is crucial in order to avoid conscious laryngoscopy, which should be limited to life-threatening situations [9].

3.3. Laryngeal mask

Three randomised controlled trials compared surfactant administration through laryngeal mask to endotracheal intubation [42,43] or CPAP alone [44]. None included premedication prior to laryngeal mask insertion and only one assessed pain/comfort as a secondary outcome. In this last study, Barbosa et al. found higher neonatal infant pain scales in the laryngeal mask group, compared to the intubated group who had received premedication with midazolam and remifentanil [43]. However, the median pain scores were comparable at baseline and after laryngeal mask removal.

In an observational study on surfactant administration through laryngeal mask, the video provided as a supplementary file (accessed at https://figshare.com/articles/Catheter_and_Laryngeal_Mask_Endotracheal_Surfactant_Therapy_the_CALMEST_approach_as_a_novel_MIST_technique/4263713) shows that the procedure can be uncomfortable, at least in some infants [45].

4. Use of pharmacological treatments during NIV

4.1. Experience in neonatal, pediatric and adult intensive care

The use of pharmacological sedation and/or analgesia during NIV is a controversial subject. Indeed, the main goal of sedation during NIV is to provide comfort and analgesia while ensuring minimal or absence of respiratory depression and impairment of the upper airway. The risk-benefit ratio has to be carefully outweighed when considering pharmacologic pain control and/or sedation in premature infants.

Recent recommendations advise to minimise stress and to prefer non-pharmacological analgesic techniques in neonates [46]. However, the use of analgo-sedative drugs is sometimes required and might even help in specific situations [47].

In the literature, around 20% of patients treated with NIV received pharmacological sedation or analgesia: 18% (266/1496) of neonates in a European prospective cohort (EUROPAIN) [48] and 19.6% (165/842) of adults in an international prospective cohort [49]. In both neonates and adults, intermittent sedation was preferred to continuous sedation [48,49]. Longrois et al. reviewed the use of sedation during NIV in adult patients: they advised against benzodiazepines use; opioids and propofol might also be deleterious during NIV due to increased collapsibility of the upper airway; dexmedetomidine and ketamine presented the most suitable pharmacological profiles [47]. In neonates, paracetamol (11%) was most frequently used, followed by opioids (6%), hypnotics (3%) and general anesthetics ($< 1\%$) [48].

To our knowledge, there is no randomised clinical trial available assessing the use of analgo-sedation during NIV in neonates. An observational prospective study in 64 preterm neonates (mean (SD) GA, 29.6 (3.3) weeks; postnatal age, 10–13 days) under CPAP reported a significant decrease in heart rate, respiratory rate and pain scales after administering a single dose of morphine ($25 \pm 12\,\mu g/kg$) [50]. Six patients (9.3%) developed delayed apnoea requiring intervention: two received naloxone, two received pharyngeal ventilation, one was intubated and one received naloxone and was subsequently intubated. Patients born < 28 weeks had higher risk of severe apnoea [50]. Similarly, a retrospective matched-cohort study in non-intubated neonates undergoing central line placement reported a significant difference in respiratory depression between morphine-treated infants (mean (SD) dose, 60 (20) μg/kg) and controls (11.6% *vs* 0%, $p = 0.02$) [51].

Overall, the risks of morphine administration at doses of 10 μg/kg and higher outweigh the benefits of pain control. However, pain and discomfort induced by NIV cannot be ignored and pharmacological alternatives such as paracetamol or dexmedetomidine might be considered if needed.

4.2. Paracetamol

In an attempt to avoid opioids or sedatives, there is a trend towards increased use of paracetamol to deal with neonatal pain [52]. For example in the German Neonatal Network, 5.6% of very low birth weight infants received paracetamol in a 2003–2009 period versus 8.1% in 2010 [53]. To our knowledge, there is no specific study reporting the effect of paracetamol use on pain or discomfort related to NIV. More generally, there are few studies on paracetamol monotherapy in neonates and especially preterm neonates. In a recent Cochrane systematic review on paracetamol use in neonates [54], it has been shown to be a poor procedural analgesic (for heel lances or retinopathy screening). On the other hand, paracetamol has a sparing effect on morphine requirements for post-operative pain management in infants born > 36 weeks [55]. This sparing effect has also been suggested in infants born < 32 weeks GA hospitalised in the NICU [56].

Concerning safety paracetamol demonstrated a good short-term tolerance profile with modest hemodynamic adverse effects and prospective data suggested good hepatic tolerance [57]. Nevertheless, long-term outcomes need to be considered. Epidemiological studies suggested associations between perinatal paracetamol exposure and long-term outcomes. Indeed, it might have a role in the development of asthma and atopy, in impaired masculinisation and in neurobehavioral outcome such as attention deficit hyperactivity disorder incidence [58]. Some of these associations could reflect reverse causality or confounding but further studies are definitely needed.

In summary, evidence is lacking to support or discourage the use of paracetamol to improve comfort in neonates with NIV.

4.3. Dexmedetomidine

To obtain conscious sedation, dexmedetomidine has been more and more used in pediatric ICUs [59]. It exhibits valuable properties: it provides sedation, anxiolysis and analgesia with no significant respiratory depression and no direct effect on the patency of the upper airways [47].

A large retrospective cohort study by Venkatraman et al. reported the use of dexmedetomidine in 202 children receiving NIV [60]. Patients received doses ranging from 0.4 to 0.8 mcg/kg/h and were treated during a median of 35 h. The target sedation level was achieved in 168/202 (83%) of patients. This study was mainly conducted in children with status asthmaticus and bronchiolitis, with only 7.9% of patients < 6 months old and no mention of neonates. In another cohort of 382 pediatric patients receiving NIV, dexmedetomidine was used at a median dose of 1 mcg/kg/h and for a median time of 45 h with well-tolerated hemodynamic effects including bradycardia and hypertension [61].

Few studies have assessed the use of dexmedetomidine in neonates and assessment occurred mainly during mechanical ventilation. A phase II/III study conducted in 42 preterm and term neonates (GA ≥ 28 weeks, weight at inclusion ≥ 1 kg) assessed dexmedetomidine for sedation during mechanical ventilation with a loading dose (range 0.05–0.2 μg/kg) followed by a maintenance dose (range 0.05–0.2 μg/kg/h), both depending on gestational age [62]. A majority of patients were adequately sedated with only 9% requiring extra sedation and no significant adverse effects were observed. Twenty percent of patients were extubated while receiving dexmedetomidine and no major adverse event was reported in this study.

A retrospective case-control study in 48 premature neonates (mean GA 25 weeks, mean postnatal age 27 h) compared sedation with fentanyl or dexmedetomidine (mean infusion rate 0.6 μg/kg/h; mean duration 12 days) during mechanical ventilation. Patients in the dexmedetomidine group had a significantly higher percentage of treatment days requiring no additional sedation (54.1% *vs* 16.5%, $p < 0.05$) and a shorter duration of mechanical ventilation (mean (SD) 14.4 (7.3) *vs* 28.4 (9.9) days, $p < 0.0001$) [63]. However, these outcomes probably reflect practices influenced by the drugs used, rather than the sole effects of each drug. In this study, dexmedetomidine infusion was not an obstacle to extubation and to spontaneous breathing since 83% of preterm neonates in the dexmedetomidine group were still receiving it at the time of extubation. There was no hemodynamic adverse effect (hypotension, hypertension or bradycardia) noted in the dexmedetomidine group and no sign of withdrawal.

Overall, dexmedetomidine could be a valuable tool for sedation during NIV in neonates. Studies addressing dexmedetomidine use in neonates are promising with an apparently good short-term tolerance in this population. However, these studies are not specific to neonatal NIV, do not address long-term outcome and contain data for a small number of patients. Hence, further efficacy and safety studies in neonates with NIV and on larger cohorts are required.

5. Conclusion

Overall, besides non-pharmacological strategies, very little robust evidence is available to guide clinical practice aiming at promoting comfort and pain control during NIV in premature infants. This underlines that unsatisfactory analgesia might be considered as the “price to pay” in order to maintain NIV. However, proper pain assessment should be systematically included in future trials dedicated to respiratory strategies because short-term respiratory benefits should not outweigh long-term adverse effects of early painful experiences. New approaches, such as nebulised surfactant or synchronisation of NIV cannot solely focus on respiratory outcomes. While results from future research are awaited, a pragmatic, common sense based approach seems reasonable in order to prevent or treat pain or discomfort in premature babies receiving NIV. Wisely choosing the best NIV delivery system and interface, improving synchronisation (or avoiding asynchrony) and parsimoniously using effective and safe analgesic and/or sedative drugs should be part of daily care in modern NICUs.

5.1. Practice points

- Non-invasive ventilation provides lung protection to premature infants with respiratory distress but it can cause pain and/or discomfort
- High flow nasal cannulas decrease the risk for nasal injury as compared to CPAP, but their respective efficacy is still debated.
- During CPAP, the use of nasal masks rather than nasal cannulas and the use of nasal barrier dressing for nasal cannulas decrease the risk for nasal injury.
- Although the effect of asynchrony during non-invasive ventilation on comfort/pain has not been assessed in premature neonates, neurally adjusted ventilatory assist improves synchrony and might improve comfort.
- Strategies currently used to avoid mechanical ventilation while administering surfactant have insufficiently studied the assessment and management of pain related to upper airway access.
- The use of opioids or benzodiazepines should be discouraged in premature infants receiving non-invasive ventilation.
- Paracetamol and dexmedetomidine are potential analgesic drugs in premature infants receiving non-invasive ventilation.

5.2. Research directions

- Currently used non-invasive respiratory support modes and interfaces should be specifically assessed for their impact on comfort and pain.
- Comparison of conventional CPAP with high flow nasal cannulas or non-invasive neutrally adjusted ventilatory assist should be performed with regard to prolonged pain and comfort.
- Propofol is a promising premedication for LISA/MIST and deserves further investigation.
- Efficacy, safety and short- and long-term and tolerance of paracetamol and dexmedetomidine to treat or prevent discomfort/pain during non-invasive ventilation should be studied in premature infants.

Conflicts of interest

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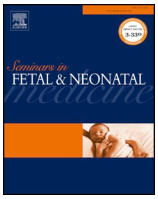

Long-term effects of neonatal pain

Suellen M. Walker[a,b,*]

[a] Clinical Neurosciences (Pain Research), UCL Great Ormond Street Institute of Child Health, United Kingdom
[b] Department of Anaesthesia and Pain Medicine, Great Ormond Street Hospital NHS Foundation Trustvd, United Kingdom

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ABSTRACT

Pain experienced during neonatal intensive care management can influence neurodevelopmental outcome and the somatosensory and/or emotional components of pain response in later life. Alterations in biological factors (e.g. peripheral and central somatosensory function and modulation, brain structure and connectivity) and psychosocial factors (e.g. gender, coping style, mood, parental response) that influence pain have been identified in children and young adults born very preterm or extremely preterm. Earlier gestational age at birth and cumulative pain exposure from tissue-breaking procedures and/or neonatal surgery influence the degree of change. In neonatal rodents, repeated needle insertion or hindpaw incision identify developmentally-regulated and activity-dependent long term alterations in nociceptive processing, and the efficacy of novel or current analgesic interventions can be compared. As prior neonatal experience and sex may influence current pain experience or the risk of persistent pain, these factors should be considered within the biopsychosocial assessment and formulation of pain in later life.

1. Introduction

Exposure to physiological and psychosocial stressors in early life can influence a range of health outcomes in later life, with adverse effects on mental and physical well-being, and alterations in the risk for future disease (eg. cardiovascular, respiratory, and gastrointestinal disorders) [1]. The need to identify and understand the mechanisms underlying effects of early-life exposures on the experience and risk of persistent pain in later life is increasingly recognized [2]. Advances in neonatal intensive care unit (NICU) management have significantly improved survival following preterm birth, but the degree and range of environmental exposures and necessary medical interventions may alter the normal development of the immature nervous system. This review will summarize clinical data reporting associations between neonatal pain exposure and neurodevelopmental outcome, somatosensory function and current pain report in childhood and late adolescence, and risk of persistent pain in later life. Laboratory studies in rodent models of tissue injury relevant to procedural and surgical interventions in NICU (repeated needle prick and hindpaw incision) that identify age-dependent mechanisms and potential preventive interventions will also be discussed.

2. Factors influencing pain sensitivity following neonatal intensive care and/or surgery

2.1. Biopsychosocial formulation of pain

The long-term impact of neonatal pain and tissue injury cannot be simply summarized as a subsequent increase or decrease in sensitivity. While nociception is the neural process of encoding noxious stimuli, pain is a complex and unpleasant sensory and emotional experience. Therefore, pain response encompasses biological factors (eg. changes in somatosensory function and nociceptive signaling), environmental and psychosocial factors (eg. sex, coping style, mood and parental response) (Fig. 1).

2.2. Population

Long-term effects of neonatal pain have predominantly been studied in NICU cohorts, but the populations vary. Infant groups may be described in terms of gestational age at birth (preterm $<$ 37 weeks gestational age, GA) and compared with term-born ‘healthy’ control groups. However, the degree of prematurity has a significant impact (eg. very preterm, VP $<$ 32 weeks GA or extremely preterm, EP $<$ 28 weeks GA). Alternatively, size may be the primary descriptor (eg. very low birth weight, VLBW; small for gestational age, SGA; intra-

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[*] Clinical Neurosciences (Pain Research), Level 4 PUW South, UCL GOS Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, United Kingdom.
E-mail address: suellen.walker@ucl.ac.uk.

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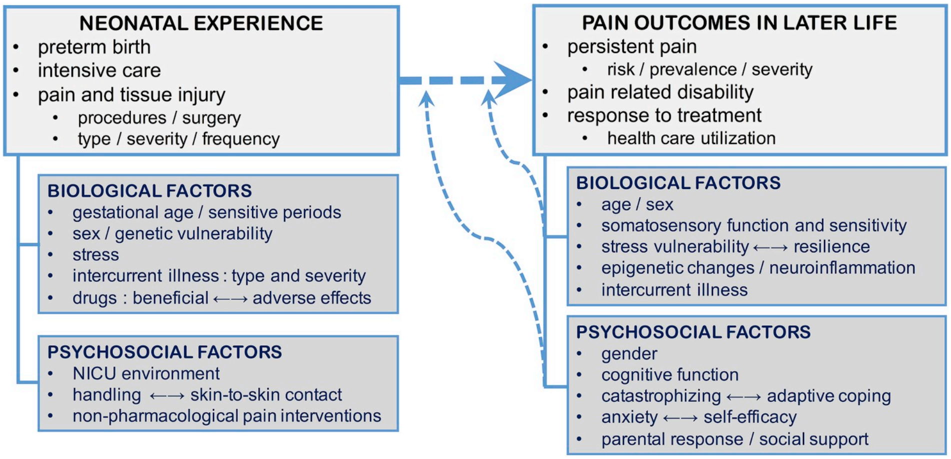
NEONATAL EXPERIENCE
preterm birth
intensive care
pain and tissue injury
procedures / surgery
type / severity / frequency
BIOLOGICAL FACTORS
gestational age / sensitive periods
sex / genetic vulnerability
stress
intercurrent illness : type and severity
drugs : beneficial ←→ adverse effects
PSYCHOSOCIAL FACTORS
NICU environment
handling ←→ skin-to-skin contact
non-pharmacological pain interventions
PAIN OUTCOMES IN LATER LIFE
persistent pain
risk / prevalence / severity
pain related disability
response to treatment
health care utilization
BIOLOGICAL FACTORS
age / sex
somatosensory function and sensitivity
stress vulnerability ←→ resilience
epigenetic changes / neuroinflammation
intercurrent illness
PSYCHOSOCIAL FACTORS
gender
cognitive function
catastrophizing ←→ adaptive coping
anxiety ←→ self-efficacy
parental response / social support

Fig. 1. Schematic biopsychosocial model of potential links between early life pain in preterm neonates and adult pain outcomes. Neonatal experience is influenced by multiple biological and intercurrent clinical confounders, as well as social and environmental factors in intensive care. In adults, biological and psychosocial factors may influence the experience or report of pain and/or modulate the long-term impact of prior neonatal experience. Factors that may have negative or positive effects on outcome are indicated with bidirectional arrows. Reproduced with permission from Walker [1].

uterine growth restriction, IUGR), and while these populations are likely to overlap with earlier gestational age, additional co-morbidities may contribute to impaired growth and adverse outcome [3].

2.3. *Pain exposure*

As the developing nervous system is vulnerable to alterations in activity, the degree of pain exposure and associated nociceptive afferent input may be expected to influence outcome. However, cumulative pain exposure during neonatal intensive care is difficult to categorize and quantify. Duration of mechanical ventilation or NICU stay have been used as retrospective proxy measures of pain exposure [4,5]. More recently, the numbers of tissue breaking procedures have been prospectively counted and shown to correlate with subsequent outcome [6]. The increased tissue injury and perioperative pain associated with prior neonatal surgery may also indicate increased pain exposure [7]. Infants born extremely preterm are a high-risk group as physiological systems are immature and management often requires prolonged intensive care, with significant pain exposure if multiple procedures or surgery are required as part of monitoring and care or for management of complications [8].

2.4. *Confounding factors*

The specific effects of pain are difficult to separate and distinguish from associated co-morbidities in clinical cohorts. The most immature and sickest neonates are likely to require additional procedural and/or surgical interventions, and potential confounders include infection or sepsis, physiological instability and stress, environmental factors and pharmacological treatments. Risks associated with the 'need for surgery' may also reflect disease severity, perioperative physiological instability, or effects of anaesthesia. Different types and dose of analgesic and sedative drugs, such as opioids and benzodiazepines, can have positive and/or negative effect on outcome, as detailed in a recent review [9]. Glucose can modulate acute behavioural responses to procedural interventions, but increased numbers of tissue-breaking procedures and higher cumulative doses of glucose/sucrose have been associated with poorer neurodevelopmental outcome and altered brain structure and connectivity [10]. While it is now widely acknowledged that untreated pain can influence neurodevelopmental outcome, and adequate analgesia is required for significant painful procedures and surgery, there is currently wide variability in the use of sedative and analgesic drugs in neonatal units [9]. The most effective and safe regimens for controlling both acute responses to noxious stimuli and for preventing adverse long-term outcome are yet to be determined.

2.5. *Follow-up age and outcome assessed*

Age at time of follow-up influences the type and sensitivity of outcome that can be evaluated. In older children and adolescents, more detailed somatosensory testing, pain history, self-reported validated questionnaires and functional neuroimaging can more fully evaluate current sensory function and pain experience. However, the degree to which biological effects associated with preterm birth persist into adulthood, or are modulated by subsequent experience and psychosocial factors can also vary [8].

3. Neonatal pain exposure and subsequent outcome

3.1. *Pain exposure and neurodevelopmental outcome*

Increased numbers of tissue breaking procedures during NICU have been associated with poorer cognitive, motor, and behavioural neurodevelopmental outcomes in infancy [6]. In extreme preterm birth cohorts, 25–30% had required neonatal surgery [7,11], and this was associated with increased rates of major neurosensory disability in childhood [11] and lower cognitive scores that persisted into late adolescence [7,8]. Effects could not be related to specific surgical procedures (most commonly inguinal hernia repair, patent ductus arteriosus ligation, bowel surgery, surgery for hydrocephalus), although it was noted that the different subgroups were relatively small [11].

3.2. *Somatosensory function following preterm birth and NICU*

Quantitative sensory testing (QST) utilizes a range of stimulus modalities (eg. thermal and mechanical) to evaluate large-fiber (A-beta) and small-fiber (A-delta and C-fiber) somatosensory function. Tests vary in intensity and can include: static measures (eg. baseline sensory thresholds); dynamic stimuli (eg. brush allodynia, repeated stimuli and perceptual sensitization); and tolerance or sensitization/habituation to more prolonged stimuli (eg. cold pressor test or altered pain report with a sustained heat stimulus).

Associations between neonatal pain experience and somatosensory function in later life vary with the population studied, age at time of evaluation, and type and intensity of the experimental stimulus [1]. Following preterm birth and neonatal intensive care, baseline thermal static thresholds showed generalized reductions in thermal sensitivity. The degree of change was greater in children born VP who required longer hospital admission than term born NICU patients [12], and in EP born children who also required neonatal surgery [13]. However, a more intense or prolonged thermal stimulus can unmask increased sensitivity: increased self-reported pain intensity (perceptual sensitization) to a more prolonged heat pain stimulus [12]; or reduced tolerance of cold pressor testing (hand immersion in 0–5 °C water bath) [5,7]. As the relative influence of neonatal biological factors and subsequent psychosocial factors may change at older ages [8], and age and sex/gender influence sensory thresholds throughout childhood and adolescence, characterizing persistent effects requires longitudinal follow-up. In VLBW or SGA young adults, no difference in thermal sensitivity was reported [14]. However, in EP young adults we found persistent group differences that were more marked following neonatal surgery, and independent of cognitive scores. In addition, sex-dependent differences had emerged with reduced baseline sensitivity predominantly in males and increased sensitivity to prolonged cold in females [7,15]. Associations between the degree of prematurity and altered somatosensory function could reflect increased vulnerability of the more immature nervous system and/or increased cumulative exposure to pain and tissue injury with longer duration of intensive care, more procedural interventions, and potential complications requiring surgery. Significant inter-individual variability in QST measures, in both control and exposure groups, highlight the need for large sample sizes to further assess the degree of difference that is clinically significant and/or associated with altered current pain experience.

3.3. Prevalence of recurrent or persistent pain

Associations between preterm birth and the prevalence of chronic pain have been sought, but differences in methodology (large epidemiological studies versus clinical cohort studies), definitions, and limited details about the type, severity and impact of pain, hamper comparison across studies [1].

Epidemiological studies demonstrate associations between increased risk of chronic pain in adulthood and different forms of early life adversity or childhood somatic symptoms [16]. In the 1958 British Birth Cohort, 288 of 7382 participants were born before 37 weeks gestation, and had a borderline significant (RR 1.26, 95%CI: 0.95–1.67) increased risk of chronic widespread pain at 45 years [17]. In the Norwegian Nord-Trøndelag Health Study, 7019 adolescents (mean age 15.8 years) completed pain questionnaires, and 44% reported chronic non-specific pain (pain at least once a week during the last 3 weeks) and 10% reported daily pain. There was no consistent association between preterm birth (80 born < 34 weeks GA between 1988 and 1994) and current pain report [18]. In both studies, the relative numbers of participants born very preterm was limited, and as with all studies evaluating long-term outcome, changes in clinical practice may hamper extrapolation to current cohorts. Since the introduction of surfactant therapy in the 1990s, survival at much earlier gestational ages has improved, and increased numbers of those born extremely preterm are now reaching adulthood.

An alternative approach is to focus on more detailed evaluation in smaller numbers within high-risk cohorts. Differences in definitions of recurrent or chronic pain contribute to conflicting results, and as recurrent pains are common during childhood and adolescence, large sample sizes will be required to detect significant differences. Based on limited items within quality of life or general health care questionnaires, current pain prevalence in VP or EP young adults has variably been reported as no different, decreased, or increased [1]. In VP and VLBW cohorts, self-reported pain increased throughout the third decade [19] when chronic pain generally becomes more prevalent, particularly in women [20]. While longitudinal evaluations in extremely preterm cohorts have identified persistent effects on cognitive, mental health and system-specific health outcomes [21,22], pain experience has not been consistently assessed. In extremely preterm young adults from the United Kingdom EPICure cohort, we found no difference in overall prevalence of recurrent pain as mild pain was common in both EP and term-born groups. However, a more detailed history identified an increased proportion of EP participants with recurrent pain of at least moderate intensity that required analgesia and interfered with activity [7].

4. Prior neonatal pain as a risk factor for future pain

Factors related to different biological and psychosocial aspects of pain experience that can influence risk of future pain can also be altered by prior preterm birth and neonatal experience. While current evidence does not support generalizations for all preterm-born children and young adults, prior experience should be included within a comprehensive pain history and form part of a personalized approach to management.

4.1. Altered somatosensory function and modulation

In the periphery, scars related to surgery or major procedural interventions in the neonatal period were associated with localized changes in sensitivity in EP young adults. Some participants reported allodynia, and QST identified both brush allodynia and sensitization to a repeated mechanical stimulus (increased pain report with a train of punctate stimuli or ‘wind-up’) adjacent to neonatal scars [7], that may increase the risk of persistent pain if further surgery is required in the same area. Although the impact of repeat surgery has not been assessed in children or adults, infant surgery in the same dermatome as prior neonatal surgery was associated with increased pain and perioperative analgesic requirements [23]. This is consistent with our laboratory studies demonstrating increased hyperalgesia following re-incision in adult rodents with prior neonatal incision; an effect that is developmentally regulated and specific to an initial injury occurring in the neonatal period (see Section 5).

Conditioned Pain Modulation (CPM) assesses the ability of a noxious ‘conditioning stimulus’ to alter sensitivity to a ‘test stimulus’ at a distant body site. Descending pathways from the brainstem tend to show tonic inhibitory effects on spinal nociceptive transmission in adulthood, although a shift to facilitation is seen with acute injury and some chronic pain states [24]. Weak inhibitory effects in childhood become more robust throughout adolescence, but were absent in 7–11 year old VP children with longer NICU admission and increased procedural pain exposure [4]. While inhibitory modulation could be evoked in the majority of EP young adults, the CPM protocol also identified a high proportion of EP females with increased sensitivity to pressure (test stimulus) and noxious cold (conditioning stimulus) in whom inhibition could not be reliably detected [15]. As impaired inhibitory CPM has been suggested as a biomarker to predict persistent pain following surgery, risk of chronic pain, or individual differences in treatment response [15,24], further evaluation in preterm cohorts is warranted, and neonatal experience should be considered when evaluating the risk of persistent post-surgical pain.

Experimental pain sensitivity has been correlated with altered structure and connectivity in central sensory-discriminative (e.g. thermal sensitivity and somatosensory cortical thickness [25]) and emotional/affective pathways (e.g. visceral sensitivity and thalamus and amygdala volume [26]). Increased procedural pain exposure in NICU and neonatal surgery have been associated with significant changes in brain structure and connectivity that include regions relevant for pain processing [27–29]. Functional MRI in children born VP who required NICU care identified increased activation in pain-relevant regions (somatosensory cortex, anterior cingulate, insula) in response to a prolonged thermal stimulus [30]. The amygdala attaches emotional significance to sensory information relayed from the thalamus, and differences in amygdala volume and connectivity influenced fear processing and emotion recognition following preterm birth [31,32]. In EP young adults, lower amygdala volume correlated with both the degree and directionality of altered thermal sensitivity (ie. decreased generalized thermal sensitivity in males, but increased sensitivity in females) [7].

4.2. Psychosocial factors and risk of future pain

Pain is a complex sensory and emotional experience, requiring a biopsychosocial approach to evaluation and management [33]. While some psychosocial factors can increase resilience or be protective (e.g. social support, active coping), others increase vulnerability (e.g. fear of pain, anxiety, catastrophizing) (Fig. 1). Very preterm children had higher pain catastrophizing scores (increased rumination, magnification and perceived helplessness in relation to pain) and parents were more solicitous, and these factors may impair the ability to cope with or self-manage pain [34]. In EP young adults, increased anxiety and pain catastrophizing correlated with increased thermal sensitivity and more intense current pain [7,15]. As child anxiety, child pain coping efficacy, and parental pain catastrophizing have predicted persistent post-surgical pain (which occurs in up to 20% of adolescents following major surgery) [35], earlier identification and targeted interventions may improve outcome.

It is now clear that sex and/or gender influences experimental pain sensitivity and the prevalence of chronic pain in adults [20] and neurodevelopmental outcome following preterm birth, but relatively few studies have compared pain-related outcomes in preterm-born males and females. At 18 months, more invasive procedures in NICU were associated with slower thalamic growth and reduced total brain volume, particularly in VP females [10]. At 7 years of age, increased neonatal procedural pain exposure was associated with lower cortisol, primarily in boys born preterm (24–32 weeks GA) [36]. In one study, reduced cold pressor tolerance in EP adolescents was predominantly due to shorter immersion times in males (13 males, 18 females) [5], while we found reduced tolerance predominantly in EP young adult females (38 males, 60 females) and additional sex-dependent differences in both experimental pain sensitivity and current pain report [7,15]. Separate reporting of outcome in males and females may further elucidate differences related to sex and gender at different ages.

5. Long-term effects of neonatal injury on nociceptive processing

5.1. Laboratory evaluations in rodent models of neonatal tissue injury

Pre-clinical evaluations of age-dependent differences in pain processing are essential for understanding acute and long-term responses to early life injury; identifying safe, effective and developmentally-appropriate analgesic interventions [1]; and may also have broader potential for identifying novel pain-resolution mechanisms [2]. The normal activity-dependent development of the nervous system is vulnerable to alterations in sensory input, with the potential for long-term alterations in structure and/or function that are not seen following the same insult at older ages. Many different laboratory models have identified persistent alterations following early life injury. Effects vary with the type and severity of stimulus, age at time of injury and assessment, and the subsequent outcome measured [1]. Here, repeated needle stick injury and hindpaw incision, which respectively model procedural pain exposure and surgical injury during the neonatal period, will be discussed. Effects of different neonatal injuries (eg. inflammation, visceral insults, traumatic nerve injury) on additional outcomes (eg. stress response) are included in recent reviews [1,37,38]. Studies are often performed in rodents that are born at an early developmental stage that has correlations with the preterm born human. Although variability in maturation across different regions of the peripheral and central nervous system limit the ability to directly translate age across species, there are similarities in the sequence of mammalian development, and effects of injury at different ages can be compared and followed to adulthood over shorter time periods in the rodent. In addition, specific confounders can be avoided or added, such as controlling for the degree of maternal separation, or evaluating effects of analgesic interventions [1].

5.2. Procedural pain exposure: repeated hindpaw needle insertion

Repeated needle insertions in one or both hindpaws and/or forepaws of neonatal rodents have been used to model repeated tissue-breaking procedures in NICU. Comparison groups include littermates exposed to a tactile stimulus only (stroke with a cotton-tipped swab) to control for the effects of maternal separation and repeated handling, and/or naïve age-matched animals. Combining results across studies is difficult as reports vary in: i) size and type of needle (eg. 28 gauge automated lancet or needle of 25–30 gauge); ii) depth of insertion (not always reported but may be restricted to the surface, be a specific depth such as 2 mm, or pass fully through the paw); iii) age and duration of exposure (daily from the day of birth throughout the first 1 or 2 postnatal weeks, i.e. postnatal day (P) 0 to P7 or P14); iv) frequency (from 4 to 30 insertions twice daily); and v) distribution of needle insertions (same unilateral hindpaw or alternate across all four paws).

While limited numbers of needle insertions in a single hindpaw (eg. 4 per day from P0 to P7) do not produce long-term changes in baseline mechanical and thermal withdrawal threshold [39], more widespread (all 4 paws) [40] and more prolonged exposures (P0 to P14) [41] have been associated with persistent sensitivity in adulthood. While one study reported no difference in adult threshold from tactile controls in both males and females [42], often the sample size is too small to evaluate sex differences [39] or males only are studied [40].

Subsequent adult incision of the neonatally-injured paw increased the duration of mechanical hyperalgesia and enhanced responses of dorsal horn neurons to pinch [39]. Paracetamol at the time of neonatal needle insertions did not alter acute hyperalgesia but reduced the duration of incision-related hyperalgesia in adulthood [43].

Following repeated needle insertion in neonatal mice (10 per day on alternate forepaws and hindpaws from P1 to P6), ex-vivo magnetic resonance imaging in adulthood found no difference in regional brain volumes between needle insertion and handling groups. However, repeated sucrose administration produced significant changes in the volume of multiple brain regions (including the hippocampus) that were exacerbated by concurrent needle prick (including somatosensory cortex, thalamus and periaqueductal gray) [44]. Functionally, repeated needle insertion has been associated with age-dependent variations in hypothalamic-pituitary-adrenal axis function and stress responsivity (as also reported in preterm ex-NICU infants) and impaired spatial memory retention in adult rats [40].

5.3. Surgical injury: plantar hindpaw incision

Incision of the skin and underlying muscle on the plantar surface of the hindpaw is an established model of postoperative pain that produces acute hyperalgesia in rodents of all ages. Alterations in withdrawal reflex sensitivity provide a measure of the degree of hyperalgesia and response to analgesia, and standardizing the length of incision to the size of the hindpaw facilitates comparison of the same relative injury at different ages [1].

Hindpaw incision in the neonatal rodent produces acute hyperalgesia that resolves within 1–2 days. Localized hyperalgesia in the previously incised paw was reported at P28-30 in males but not females [45]. Longitudinal studies have shown emergence of generalized thermal and mechanical hypoalgesia in all paws at older ages, associated with a shift in descending modulation from the normal bimodal pattern of facilitation or inhibition (depending on stimulus intensity) to predominantly inhibition [1]. This generalized distribution of reduced sensitivity has parallels with clinical QST findings in preterm-born children who required neonatal surgery and/or intensive care (Section 3.2).

Neonatal incision also has a long-term impact on the response to re-injury in later life. Incision in the first postnatal week, but not at older ages, increases both the degree and duration of re-incision hyperalgesia in adult male and female rodents. Thus, there is a ‘somatosensory memory' of the early life injury [46,47]. Spinal cord mechanisms contribute to persistent effects with alterations in synaptic signaling resulting in increased excitation and decreased inhibition [48,49]. Interactions between neurons and glia also alter nociceptive sensitivity within the spinal cord, and priming of spinal microglia by neonatal injury contributes to increased microglial reactivity, sensitization and hyperalgesia following re-incision in adulthood [46]. While the same degree of re-incision microglial reactivity and behavioural hyperalgesia is seen in both male and female rodents, responses to microglial inhibitors are sexually dimorphic and effective in male rodents only [50].

Plantar incision allows the comparative efficacy of different analgesic interventions to be assessed. Acute hyperalgesia following neonatal incision can be dose-dependently prevented by a range of analgesic interventions [1]. Sciatic nerve local anaesthetic blockade at the time of neonatal incision has preventive effects on several outcomes including: acute hyperalgesia, alterations in spinal excitatory signaling, generalized increases in reflex threshold and altered descending modulation in adulthood, and the enhanced response to re-incision [1,47,49]. This supports the hypothesis that long-term alterations in nociceptive function are activity-dependent and triggered by increased nociceptive input. By contrast, systemic and intrathecal doses of morphine that effectively control acute hyperalgesia during the period of neonatal administration, do not prevent the long-term changes in reflex threshold or re-injury response [47]. Neonatal incision alone did not alter morphine efficacy in adolescence [45] or early adulthood [47], but morphine administration in the absence of tissue injury has been associated with long-term changes in efficacy [47]. This suggests that using morphine for neonatal sedation in the absence of pain or injury may produce different long-term effects than when used for analgesia. This further highlights the need for ongoing research to optimize practice protocols for analgesia and sedation during neonatal intensive care [9].

6. Conclusions

Preterm birth, neonatal intensive care and neonatal surgery are associated with adverse long-term effects on neurodevelopmental and somatosensory outcome, that are also influenced by gestational age at birth. Management of neonatal pain needs to consider modulation not only of acute behavioural and physiological responses, but also the potential long-term effects of pain and injury, and the relative risk-benefit of different analgesic and sedative interventions. Preclinical models of neonatal tissue injury confirm specific developmental and activity-dependent alterations in nociceptive function that persist into adulthood, and that can be modulated to varying degrees by different analgesics. Further evidence is required to achieve consensus regarding the safest and most effective interventions for pain in neonates, to minimize acute physiological and behavioural distress and improve long-term outcome. For children and adolescents with significant early life pain exposure, recognition of risk factors for altered sensory and emotional responses to subsequent pain may identify those at increased risk of persistent pain who would benefit from targeted interventions.

6.1. *Practice points*

- Minimizing the number of procedural interventions where possible, regular assessment of pain and sedation, and providing procedural and perioperative analgesia are important components of management in neonatal intensive care.
- The evaluation and management of pain requires consideration of biological, environmental and psychosocial factors that influence the sensory and/or affective components of pain.
- Prior neonatal experience should be considered when assessing pain and future injury response in infants and children born preterm.

6.2. *Research directions*

- Further longitudinal follow-up with standardized outcomes is required to quantify the long-term impact of neonatal pain and identify subgroups of preterm-born children and adolescents at risk of persistent pain.
- In clinical cohorts, comparison of outcome in males and females is required to identify sex and/or gender differences in the biopsychosocial aspects of pain response.
- Preclinical studies are essential for understanding specific effects on nociceptive pathways, and evaluating potential mechanism-based and/or sex-dependent preventive interventions.
- Prospective clinical trials are needed to increase the quantity and quality of current evidence and develop protocols for minimizing the long-term effects of pain in early life.

Conflicts of interest

None declared.

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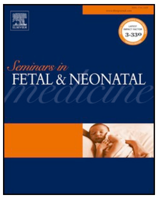

Pain and distress management in palliative neonatal care

Lars Garten[*], Christoph Bührer

Department of Neonatology, Charité - Universitätsmedizin Berlin, Berlin, Germany

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ABSTRACT

Palliative care concentrates on preventing and relieving suffering by reducing the severity of disease symptoms. Consistent treatment of pain and distress must therefore be an integral component of every palliative care concept. In this review non-pharmacological and pharmacological measures for pain and distress management in the context of palliative neonatal care are summarised. Furthermore, recommendations are given focusing on two special palliative neonatal care settings: compassionate extubation and withdrawing artificial nutrition and hydration.

1. Introduction

Palliative neonatal care is person- and family-centred care provided for a neonate with a progressive, advanced, life-limiting disease for whom the primary goal is to optimise the quality of life [1]. The evidence base in pediatric palliative care is not robust and there is a paucity of evidence specific to neonates. Accordingly, for this review on pain and distress management in palliative neonatal care we aimed to integrate published scientific research evidence with clinical expertise.

Among many other factors such as hunger and thirst, over-stimulation through noise and light, or separation from parents, pain is the leading cause of physical and psychological distress reducing the quality of life of neonates receiving palliative care. Bringing pain and distress in neonates with life-limiting conditions under control therefore has to be a core skill of every multiprofessional team caring for these vulnerable patients.

Knowledge about the physiology, diagnostics and therapy of neonatal pain has grown steadily. National and international recommendations on pain management for newborns who need intensive care have been published [2]. However, all these recommendations are based on research data of newborns under non-palliative care. As long as there are no specific studies for symptom assessment and treatment in newborns in palliative care situations, pain and symptom control must follow the basic principles that have been published for all neonates cared for in neonatal intensive care units. The following aspects of pain and distress management should be incorporated in any palliative neonatal care concept:

- The basis of symptom control in neonatal care is a form of care that is exclusively directed to the infant's individual basic needs (e.g. the need of contact to parents by means of holding or skin-to-skin care).
- An important goal of pain management is to prevent pain; it is more difficult to try to control pain once it has recurred.
- All symptoms of distress and pain should be assessed regularly - ideally by means of a suitable and validated assessment scale.
- Depending on the current symptoms, non-pharmacological as well as additional pharmacological analgesic measures are provided to achieve optimal symptom control.
- The effectiveness of non-pharmacological and pharmacological measures can be further optimised by a general reduction of external stimuli such as light, noise, or cold stress.

2. Assessment of pain and distress

Since the late 1980s, more than 40 different assessment scores for acute, procedural pain in newborns have been validated and published [3]. However, acute, procedural pain is not a priority in palliative neonatal care. Rather, prolonged/chronic pain is the most frequent and challenging condition in the context of palliative care. For prolonged/chronic pain, only three pain scores are currently validated for neonates:

- Echelle Douleur Inconfort Nouveau-Né scale (EDIN scale) [4].
- Neonatal Pain, Agitation and Sedation Scale (N-PAS scale) [5,6].
- COMFORTneo scale [7].

However, all so-called “pain scales” are not specific for pain [8]. High scores may represent pain as well as distress caused by hunger,

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[*] Corresponding author. Klinik für Neonatologie, Charité - Universitätsmedizin Berlin, Augustenburger Platz 1, D-13353, Berlin, Germany.
E-mail address: lars.garten@charite.de (L. Garten).

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agitation, or the desire for physical closeness. It would be more correct to speak of "distress" scales in general rather than "pain" scales. Consequently, elevated pain scores in a newborn baby should always be interpreted in the clinical context by the medical team. Whenever possible, further assessments by other team members (e.g. physiotherapists), but also by the infant's parents, should be considered. Finally, it should be noted that so far no neonatal pain scale has been explicitly validated for use in patients under palliative neonatal care.

3. Non-pharmacological interventions

3.1. Behavioural and physical strategies

Various non-pharmacological measures can be used in neonates to reduce stress reactions in *acute procedural* pain [9,10]. Behavioural (e.g. swaddling, facilitated tucking) and physical (e.g. kangaroo care, breastfeeding, non-nutritive sucking) strategies have been shown to significantly reduce physiological and behavioural pain reactions of newborns after acute procedural pain [11]. The combination of several non-pharmacological measures is superior to the isolated use of non-pharmacological measures with regard to the pain modulating effect [12]. The use of non-pharmacological measures should be a consistent part of the daily care of newborns receiving palliative care. Within the framework of non-pharmacological measures, there is a valuable opportunity to actively involve parents in a central and essential aspect of their infant's care, namely pain and distress management.

3.2. Sucrose for analgesia

The soothing and pain-modulating effects of orally administered sugar on infants have long been known and the use of sugar substances was accordingly already an integral part of traditional infant care in the past. Today administration of oral sucrose in combination with and without non-nutritive sucking is the most frequently studied non-pharmacological intervention for *acute procedural* pain relief in neonates [13]. Sucrose is effective for reducing procedural pain scores from single events such as heel lance, venepuncture and intramuscular injection in both preterm and term infants but does not alter nociceptive brain activity [14]. No serious side effects or harms have been documented with this intervention. The pain modulating effect after oral administration of sucrose is superior to the isolated use of non-pharmacological measures in almost all studies. The effect of various non-pharmacological measures can be increased by the additional administration of sucrose/glucose. It is therefore recommended - whenever possible - to combine non-pharmacological measures with oral sucrose [15].

4. Pharmacological pain management

No analgesics with proven efficacy and safety other than opioids are currently available for the systemic treatment of severe pain in neonates. Dosing regime and route of administration of drugs used in palliative neonatal care are summarised in Table 1.

4.1. Opioids

In newborn infants, there is a high intra- and inter-individual variability in the metabolism of most opioids. For this reason, it is not possible to provide general or weight-related standard and/or maximum dosages, regardless of the type of application used. The dose of opioids required for optimal symptom control must be titrated individually to the effect. The required dose must be adjusted repeatedly if tolerance develops during the course of therapy. Of note, acute, painful procedures such as capillary blood collection [16] or endotracheal suction [17] are not treated sufficiently by opioids in preterm infants. Especially in premature infants, it is therefore advisable to apply non-pharmacological measures in combination with oral sucrose as a supplement to treat procedural pain, even during on-going continuous opioid infusion.

4.1.1. Routes of opioid administration

Parenteral. Intravenous administration of opioids has the advantage of rapid onset of the analgesic effect, simple dosage titration at the beginning of long-term therapy, and high and uniform bioavailability. The following aspects are to be considered if opioids are applied parenterally:

- Prolonged pain should be treated by continuous intravenous opioid infusion to ensure stable plasma levels and avoid under- or overtreatment due to fluctuating plasma levels.
- Bolus injections of opioids in newborns should only be used at the beginning of long-term therapy for initial loading and for the treatment of breakthrough pain.
- Opioid bolus injections should be administered as a short infusion over a period of approximately 5–10 min to prevent adverse effects such as severe arterial hypotension (especially in premature infants), laryngospasm, or severe thoracic rigidity.

Oral. In palliative care any medication should be administered in the simplest, safest, most effective and least unpleasant way. If no (central) venous access is in place, oral morphine solution can be used alternatively to opioid infusions. Following oral dosing, morphine has a significant first-pass effect in the liver. An oral-to-parental potency ratio of approximately 3:1 is commonly encountered during chronic administration.

Intranasal. In palliative neonatal care, intranasal drug administration is an alternative option for delivering opioids to patients without vascular access (off-label use). Most study data for intranasally applied opioids in the pediatric setting is currently available for fentanyl [18]. There is currently only one publication on the use of intra-nasal fentanyl for symptom control in palliative care in newborns and infants up to 6 months old [19], demonstrating that the use of intranasal fentanyl is safe and effective. Recommended single doses are 1–3 µg/kg, leading to a therapeutic effect within 5–10 min. The standard fentanyl injection solution (0.1 mg/2 ml) can be used for intranasal administration. Application by means of a mucosal atomisation device (MAD) as used in older children is not practicable for newborns as the volumes applied are too small. Intranasal fentanyl appears to be particularly suitable for symptom control in newborns cared for under palliative care immediately after birth in the delivery room.

For intranasally applied sufentanyl, only a few pediatric series with a small number of cases have been published so far, and for all other opioids no data on intranasal administration are available.

Subcutaneous. Subcutaneous administration of opioids can be an alternative to parenteral administration in newborns who cannot receive oral or intranasal opioid therapy. Subcutaneous opioids can be administered both as bolus for acute pain and as continuous infusion for prolonged/chronic pain. A commercially available intravenous cannula (24 or better 26 G) or a special subcutaneous cannula can be used for infusion access. The subcutaneous access should be exchanged every 48–72 h.

Rectal. The rectal administration of opioids is viewed with caution, due to the high variability of rectal absorption. It may be useful in the home care of the dying infant when no other route is available.

Transdermal. The transdermal application of fentanyl or buprenorphine in chronic and stable pain conditions is increasingly used in pediatric palliative care [20] while there are no reports in newborns. In our experience, the use of an opioid patch is feasible in neonates in selected individual cases when considering the following aspects:

- Opioid patches should only be used when symptoms of pain are stable.

Table 1
Dosing regime and route of administration of drugs used in neonatal palliative care.

	IV bolus	IV continuous	subcutaneous	oral	per rectum	intranasal	buccal
Morphine	0.05–0.1 mg/kg every 3–6 h	loading dose: 0.05–0.1 mg/kg starting dose: 0.01–0.02 mg/kg/h	For bolus und continuous infusion: see IV dosing regime	0.1–0.2 mg/kg every 3–6 h	0.1–0.2 mg/kg every 3–6 h	–	0.1–0.2 mg/kg every 3–6 h
Fentanyl	2–3 µg/kg every 1–4 h	loading dose: 2–3 µg/kg starting dose: 1–2 µg/kg/h	For bolus und continuous infusion: see IV dosing regime	–	–	1–2 µg/kg every 1–4 h	1–2 µg/kg every 1–4 h
N-Methylnaltrexone	0.15 mg/kg every (12-) 24 h	–	0.15 mg/kg every (12-) 24 h		–	–	–
Acetaminophen	7.5 mg/kg every 6 h	–	–	–	–	–	–
Esketamine	0.5–1 mg/kg* (e.g. for breakthrough pain)	loading dose: 1 ml/kg starting dose: 0.2–0.5 mg/kg/h	For bolus und continuous infusion: see IV dosing regime	2–4 mg/kg* (e.g. for breakthrough pain)	2–4 mg/kg* (e.g. for breakthrough pain)	2–4 mg/kg* (e.g. for breakthrough pain)	2–4 mg/kg* (e.g. for breakthrough pain)
Midazolam	0.05–0.1 mg/kg every 2–4 h	loading dose: 0.05–0.1 mg/kg starting dose: 0.1–0.2 mg/kg	For bolus und continuous infusion: see IV dosing regime	0.1–0.3 mg/kg every 2–4 h	0.1–0.3 mg/kg every 2–4 h	0.1–0.3 mg/kg every 2–4 h	0.1–0.3 mg/kg every 2–4 h
Phenobarbital	5 mg/kg every 24 h	–	–	5 mg/kg every 24 h	5 mg/kg every 24 h	–	–
Clonidine	–	0.5–2.5 µg/kg/h	–	2–4 µg/kg every 4–6 h	–	–	–
Dexmedetomidine	–	loading dose: 0.5 µg/kg starting dose: 0.3–1.0 µg/kg/h	–	–	–	–	–

Abbreviations: IV, intravenous.
Note: off-label use and off-label-route administrations are not shown separately.
* Esketamine: single doses can be used for e.g. *short time* painful procedures or acute breakthrough pain.

- Possible pain peaks (e.g. during re-positioning, endotracheal suction, etc.) are not covered by the opioid patch, necessitating additional measures.
- In newborns, use of the smallest fentanyl patch size (25 µg/h) available is recommended. In the case of a newborn weighing 3 kg, for example, 1/4 of the fentanyl patch (fentanyl patches can be cut) is then applied to the skin of the child, which corresponds to a fentanyl release of approximately 6 µg/h (or in this case 2 µg/kg/h).
- Fentanyl blood levels rise slowly when using transdermal application. Adequate analgesia can be achieved approximately after 12–24 h, and a steady state is reached 24–72 h after application of the patch.
- After removal of the patch, the effect fades slowly (approximately 12–18 h after removal). The skin area employed should remain free of new patches for 7 days afterwards.

4.1.2. Antagonisation of opioid side effects

Clinically significant side effects of opioids in newborns under palliative care include inhibition of intestinal motility via peripheral µ-receptors and urinary retention. Other side effects such as respiratory depression, thoracic rigidity, laryngospasm, hypotension and bradycardia play a minor role in the palliative context. Therapy approaches for the prevention or treatment of opioid-induced side effects show a very variable success in practice. In adult patients the opioid receptor antagonists, naloxone and methylnaltrexone are used increasingly to specifically antagonise opioid-induced side effects. Overall, no sufficient study data are available for the neonatal age for prophylaxis and treatment of side effects under opioid therapy.

Naloxone. Naloxone acts as a competitive, pure antagonist at central and peripheral opioid receptors. It can thus antagonise opioid-induced side effects mediated via peripheral opioid receptors. However, since naloxone crosses the blood-brain barrier, it also antagonises opioid-induced central analgesia. There have been several attempts in the past to treat opioid-induced side effects by systemic co-medication of low-dose naloxone. Published reports lack sufficient homogeneity to allow for any conclusions to be drawn. At higher doses (> 1 µg/kg/h), antagonisation of the central nervous system analgesic opioid effect must be expected. This adverse effect has even been described in a study on the use of orally administered low-dose Naloxone [21].

Peripherally Acting, µ-Opioid Receptor Antagonists (PAMORAs). Peripheral opioid receptor antagonism using substances from the class of PAMORA (Peripherally Acting, µ-Opioid Receptor Antagonist) represents a promising therapeutic concept. PAMORAs have restricted ability to cross the blood-brain barrier because of their polarity and low lipid solubility. Thus, PAMORAs cannot antagonise the opiate-induced central analgesia but can specifically block peripheral opioid receptors. To date only a few case reports on the use of the PAMORA N-methylnaltrexone in children - two of them in neonates (off-label use) [22,23] - and three smaller case series have been published. In selected individual cases we use a subcutaneous or intravenous single dose of 0.15 mg/kg N-methylnaltrexone for newborns with opioid-induced urinary retention or constipation/subileus (off lable use). If the treatment was successful after the first application and when the opioid-induced symptoms persist, we repeat the administration after 12–24 h at the earliest. Comparable to study results from adults, our limited anecdotal impression is that a response in about half of the patients can be expected.

There are currently no published reports on the use of orally administered PAMORAs (for example, naloxegol) in children.

4.2. Non-opioid analgesics

Currently, there is insufficient scientific evidence on analgesic efficacy or safety for the use of acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), ketamine or transdermally administered local anaesthetics in neonates. However, as these drugs are administered in “eminence- and experience-based” practice not only in children but also in newborn infants, some information concerning these substances will be provided.

4.2.1. Acetaminophen (paracetamol)

Oral and rectal. All randomised placebo-controlled studies published to date did not demonstrate any analgesic effect of acetaminophen after rectal or oral administration in newborns. Even when using high dose regimens (single dose up to 40 mg/kg), they were not superior to placebo in terms of measured pain reduction. There is currently no evidence of justified routine use of oral or rectal acetaminophen as monotherapy or in combination with opioids for analgesia in newborns [24].

Parenteral. The first randomised, placebo-controlled double-blind study for parenteral use of acetaminophen in newborns (> 36 weeks of pregnancy) and infants (maximum age 365 days of life) was published in 2013 [25]. In this study a morphine-saving effect of acetaminophen (opioid co-administration, 30 mg/kg/d intravenous in 4 single doses) during the first 48 h after surgery could be demonstrated. In addition, Härma et al. [26] showed a morphine-saving effect of parental administered acetaminophen also in premature babies under 32 weeks of gestation.

4.2.2. Non-steroidal, anti-inflammatory (NSAID) agents

NSAIDs theoretically represent an interesting alternative to opioid therapy for mild to moderate pain. In particular, the potential avoidance of opioid-induced respiratory (apnoea), gastrointestinal (ileus) and uro-dynamic (urinary retention) side effects would be of high clinical relevance. At present, however, there is insufficient evidence on analgesic efficacy for the use of NSAIDs as analgesics in newborns. Attention must be paid in all patients with kidney function impairment if an individual decision is made to start treatment with a NSAID as part of palliative neonatal care. NSAIDs are capable of significantly inhibiting prostaglandin-dependent renal function in newborns. In the case of impaired kidney function, which leads to additional strain on the child, for example via over-hydration, a dose reduction of the NSAID may be sufficient in some cases, but often the treatment must be discontinued completely.

4.2.3. Esketamine

There are few studies on the efficacy and safety of esketamine in children treated for acute painful procedures. For newborns, only a few case reports and smaller case series on isolated individual doses of esketamine have been published, but no randomised, placebo-controlled studies that have investigated the efficacy and safety of prolonged esketamine therapy. Within the framework of palliative care, esketamine can be helpful in individual patients with pain that has responded poorly to the usual measures of opioid dose escalation and other adjuvants. We usually start an intravenous long-term therapy with a loading-dose 1 mg/kg slow push (10–15 min), followed by continuous infusion at a rate of 0.2 mg/kg/h and titrate up to approximately 0.5 mg/kg/h. Tolerance development may also occur under esketamine, so an increase in dose may be necessary in the course of the disease.

Esketamine can also be administered orally, subcutaneously, rectally and intranasally in the palliative care setting (off label use). Bioavailability after oral administration is very low at 15–20% due to a pronounced first-pass effect, therapeutic plasma levels being only reached after 20–30 min after oral administration. Subcutaneous bolus injections should always be applied as short infusions, otherwise pain and tissue damage may occur at the injection site. Subcutaneous long-term therapy using an infusion pump is also possible. The intranasal application is only suitable for bolus administration (start of anaesthesia approximately 5–10 min after application).

4.3. Regional anaesthetics

4.3.1. Infiltration anaesthesia

Local anaesthetics can be used for managing severe painful skin-breaking interventions (e.g. thoracic drainage, biopsies or punctures). Lidocaine (maximum dose 7 mg/kg), levo-/bupivacaine (maximum dose 2–3 mg/kg) and ropivacaine (maximum dose 3–4 mg/kg) are suitable local anaesthetics for use in neonates.

4.3.2. Transdermal application (ointment/cream/plaster)

The transdermal use of local anaesthetics in the form of a cream is widespread in pediatrics, effectiveness and safety having been proven for children 5 years and older. An analgesic effect in peripheral and central venepuncture, intramuscular injection and lumbar puncture was observed also in infants as young as 3 months. For infants under the age of 3 months, there are little data on effectiveness and safety.

4.3.3. Peripheral or central nerve blocks

Peripheral and central regional anaesthesia procedures have also enjoyed increasing popularity in recent years in the peri-operative care of newborns. These procedures are effective and safe in the hands of the experienced physicians. However, these “acute” techniques play only a minor role in palliative neonatal care.

5. Sedation in palliative neonatal care

In addition to adequate pain therapy, palliative care also includes the consistent prevention and treatment of other distress such as restlessness and agitation. In spite of minimization of noise, light, sleep disturbances, and other negative stimuli for the infant, pharmacological sedation is often indispensable, especially in end of life situations. In general, the targeted level of sedation should be the lowest that relieves distress. Conscious sedation, where the infant is calm and able to interact with her or his parents, is often considered the ideal level of sedation. In case of intense distress, severely refractory symptoms, or anticipated death within hours, continuous deep sedation may be indicated. In the absence of controlled trials evaluation sedatives in palliative neonatal care, the drug choice is largely empirical. Medications widely used to deliver sedation in palliative neonatal care are: opioids, benzodiazepines, barbiturates, and fairly recently alpha2-adrenoreceptor agonists.

5.1. Opioids

While opioids are often used expressly for their sedating properties in acute neonatal intensive care situations (e.g. in postoperative care), they are not very effective in producing reliable, prolonged sedation in severely distressed infants under palliative care. In these challenging situations we recommend combining opioids with specific sedatives such as benzodiazepines. For further information on opioids see 4.1.

5.2. Midazolam

Midazolam was one of the first benzodiazepines reported to be used for sedation in palliative care. It has a rapid onset and short duration of action, facilitating titration. Parental sedation with midazolam is recommended to be started with a loading dose of 0.05–0.1 mg/kg, followed by continuous infusion of 0.1–0.2 mg/kg/h. However, especially in the non-hospital setting oral, rectal, intranasal, or subcutaneous application of midazolam may be indicated.

5.3. Phenobarbital

Phenobarbital may be used alternatively to midazolam. In the context of sedation in palliative neonatal care phenobarbital should be given preferably orally (5 mg/kg/d), as absorption is slow, therefore severe side effects are not to be expected.

5.4. alpha2-adrenoreceptor agonists

Applied systemically, alpha2-adrenoreceptor agonists have a sedative and anxiolytic effect. In pediatrics, they are used for pre-medication before surgery, for symptomatic therapy in opioid withdrawal, for sedation in mechanically ventilated patients or ahead of invasive procedures. Very little data is available on the use of alpha2-adrenoreceptor agonists in neonates [27,28]. The studies available so far prove a sedative effect also in newborns. Clonidine and dexmedetomidine are thought to be safer than opioids with regard to their acute side effect profile. In distressed, agitated newborns treatment with clonidine or dexmedetomidine can therefore be considered in individual cases (off label use). Side effects of alpha2-adrenoreceptor agonists include bradycardia, hypotension and oliguria/anuria caused by a decrease in renal perfusion.

6. Special aspects of symptom control

6.1. Compassionate extubation

Particularly in newborns, in whom a relevant period of spontaneous self-breathing can be expected after compassionate extubation, careful preparation is necessary in order to be able to counteract in a prophylactic manner potentially occurring distressful symptoms. The main objectives of palliative care of a neonate in the context of compassionate extubation should therefore be:

- Anticipation of pain and terminal agitation as well as prophylactic or rapid treatment thereof.
- Prevention or rapid therapy of dyspnoea (mostly caused by stridor after extubation or rarely by excessive broncho-pulmonary secretion after long-term ventilation).

Agitation and pain can significantly increase the work of breathing after mechanical ventilation and compassionate extubation. In the course of this, physical exhaustion can occur, which means additional distress for the dying child. Consistent analgesia and sedation can counteract this and should therefore have the highest priority. Opioid therapy to prevent pain and distress caused by acute dyspnea should be started before withdrawal of mechanical ventilation and compassionate extubation. Benzodiazepines may be used as anxiolytics or as an adjuvant to an opioid analgesic. Opioids and benzodiazepines appear paradoxically to not hasten inevitable death after ventilator withdrawal [29].

Neuromuscular blocking agents (NMBAs) feign freedom from pain and inner peace, the risk of under-treatment with analgesics and/or sedatives in relaxed patients being very high [30]. Having these risks in mind, there are very limited conditions in which the use of NMBAs can be reasonable. NMBAs should never be used as a sole agent and deep analgo-sedation should be warranted. Sometimes NMBAs are continued for compassionate extubation with the goal of preventing gasping at the end of life. Gasping is a physiological process (‘reflex’) that occurs to varying degrees in every natural dying process. According to current knowledge, terminal gasping is not associated with distress and it cannot be prevented by the application of opioids or sedatives.

In very rare exceptional cases after discontinuation of ventilation excessive respiratory secretion can occur in newborn infants. Post-extubation stridor can give rise to the parents' perception that their child is choking and suffering. The following measures can be considered to address these distressing symptoms [31]. Six hours before compassionate extubation, enteral feeding should be stopped and parenteral fluids reduced, overhydrated patients should be dehydrated with furosemide. At the same time administration of sedatives (for distress) and opioids (for pain and/or dyspnea) should be continued or started. Especially in neonates with previous episodes of a stridor after extubation, methylprednisolone should be given in anticipation of stridor after extubation.

Hypoxia acts as an additional “natural sedative”. We therefore reduce oxygen supplementation to FiO2 0.21 before terminating mechanical ventilation and generally do not use oxygen supplementation after compassionate extubation.

6.2. Withdrawing artificial nutrition and hydration

In neonatal intensive care withdrawal of life-sustaining treatment consists predominantly of withdrawal of assisted ventilation or pharmacological support for the cardiovascular system. However, when critically ill newborns ‘linger’ after withdrawal of life-sustaining intensive care treatment, with continued neurological impairment and poor long-term outcome, the withdrawal of artificial nutrition and hydration may become a consideration [32]. Although the practice is emerging as an accepted part of palliative care in adults, withdrawal of artificial nutrition and hydration is a significant challenge for practitioners in neonatal medicine [33].

Studies in adults have shown that death after withdrawal of artificial nutrition and hydration is not caused by starvation but by dehydration. Dehydration in end of life situations leads to a reduction in nausea, vomiting, diarrhoea and urine production, which is associated with less distress [34,35]. Furthermore, parenteral nutrition and hydration in end of life situations often contributes more to the increase in suffering (e.g. pulmonary oedema caused by fluid overload can cause severe shortness of breath). The distressing feeling of thirst does not correlate with the amount of fluid supplied but with the degree of dryness of the oral mucosa. In conclusion, continuing artificial nutrition and hydration in many neonates receiving palliative care may not always be the patient’s best interest and therefore not indicated, while treating thirst through adequate oral care is always necessary. Liberal use of analgesics (opioids) and sedatives (benzodiazepines) in addition to sufficient oral care should prevent most distressing symptoms. In a retrospective study by Hellmann et al. [36], the median time to death after discontinuation of parenteral nutrition and fluid intake in newborns was 16 days (minimum 2 to maximum 37 days).

However, as long as a newborn with a life-limiting condition likes to be fed orally, enteral nutrition should not be stopped [37].

Practice points

- Prevention of pain and distress is the most effective way of successful pain and distress management. In palliative neonatal care all diagnostic and therapeutic measures should be reviewed carefully for the following question: Do they improve the patient's quality of life?
- Regular distress and pain assessment by means of an assessment scale should be guaranteed for all neonates receiving palliative care.
- Depending on the current symptoms, non-pharmacological as well as pharmacological analgesic measures are provided to achieve optimal symptom control.
- The effectiveness of non-pharmacological and pharmacological measures can be further optimised by a reduction of external distressing stimuli (e.g. light, noise, or cold stress).
- Within the framework of non-pharmacological measures, parents should get the opportunity to be involved in pain and distress management (e.g. by providing comforting touch).
- Anticipation and consistent treatment of pain and distress are essential when withdrawing mechanical ventilation or artificial nutrition and hydration.

Research directions

- Clinical reliability and validity of existing assessment tools for pain (and/or distress of other sources) in neonates receiving palliative neonatal care. Is there a need for adaption of assessment tools for pain/distress when used in palliative neonatal care? Do we need new assessment tools for pain/distress in these challenging situations?
- Improving knowledge about efficacy and safety of (non-opioid) drugs such as ketamine, NSAID, or acetamoniphen when used in neonatal palliative care situations.
- Observational studies inquiry into pain and distress management in special palliative neonatal care situations [e.g. end-of-life care (i) in the delivery room, (ii) at the limits of viability, (iii) after compassionate extubation, or (iv) after withdrawal of artificial nutrition and hydration].

Conflicts of interest

There are no conflicts of interest to report.

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